Dealing with the Societal Implications of DOE Science

Workshop on Integrating Societal Implications into Science

May 1–2, 2006

Mariott Westfields Conference Center
Chantilly, Virginia

Sponsored by the
U.S. Department of Energy
Office of Science

Prepared by the Genome Management Information System, Oak Ridge National Laboratory

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Executive Summary

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A workshop was convened by the Department of Energy (DOE) May 1–2, 2006, in Chantilly, Virginia, to discuss a new program that will explore societal issues arising from DOE studies in nanotechnologies and synthetic genomics. The new program, provisionally named "ISIS" (Integrating Societal Implications into Science) is intended to be broader than ELSI (Ethical, Legal, and Social Issues), the long-running effort from which it derives. The explicit intention of its developers is to interweave thinking about scientific activities with explorations of their potential societal implications as much as possible right from the outset. This approach will be applied first to nanotechnology and synthetic genomics and, over time, will expand to other DOE Office of Science activities. A principal aim is to break down distinctions among science practitioners and those exploring societal implications. ISIS starts with the explicit assumption that society, including scientists and the sciences, benefits directly from considering societal implications ahead of time and at each stage of the research process. While this is not an easy proposition to demonstrate, ISIS will try to make the case convincingly.

The focus of the Chantilly workshop was the intermediate-range "issue spaces" (a term coined to convey a set of potential ELSI issues arising from a particular research area) for nanoscience and synthetic biology. The National Nanotechnology Initiative (NNI) has existed for a couple of years now, with many federal agencies participating. Another major effort, funded principally through the National Science Foundation and the Environmental Protection Agency, is looking at health and safety issues, so this workshop took a longer view. Thus, its aims were to

- Explore intermediate-range issue space for nanosciences and nanotechnology.
- Explore intermediate-range issue space for synthetic biology.
- Discuss the nature of a response capability for future challenges the Office of Science might face.

The 21st Century Nanotechnology Research and Development Act, Public Law 108-153, which authorizes NNI, requires agencies supporting nanotechnology research to consider societal implications, particularly those involving safety and health.

Ray Orbach (Director, Office of Science) discussed integrating ethics at the beginning of a research program. Noting similarities to Office of Science integrated safety management (ISM), where safety is built into programs from the beginning, he said that doing so is cheaper, more effective, and fairer to workers than waiting for an accident to happen and then trying to fix things. Ethics should be treated similarly. Ethics management should enhance the science, and the relationship between the two should be supportive, not punitive. Identifying issues that we will face in defining this territory is important for future integration. The Office of Science believes this essential feature of its function will make nanotech and other realms of advanced science that DOE supports more exciting and productive.

Nanoscience and Nanotechnology

First, what is nanoscience? Its unifying criterion involves objects with at least one dimension on the order of 1 to 100 nanometers (nm). Beyond that, the applicable "rules" seem to be:

- Nano is small—1/100,000 the width of a human hair.
- Nano is not new.
- Nanostructure properties vary with size. This is a controversial definition; for many it is not really nano unless properties do vary with size.
- Nano is where biology meets nonbiology.
- Nanomaterials are very sensitive to changes in structure.

Nanoscience is not one thing but will be many; thus, focusing exactly on the specific topics being discussed and the science reality as we know it will be critically necessary. The current regulatory framework will be strongly challenged by nanotechnologies. How can the *unknown* be regulated? A predictable contentious issue will be intellectual property rights. NNI reports that the federal government provided $1.3 billion to nanotech efforts in 2006. Already, at least 1200 startups have launched to capitalize on this investment. The Patent and Trademark Office (PTO) now is trying to figure out what "nano" is. The NNI definition requires a size range of 1 to100 nm, with unique phenomena that enable novel applications. PTO uses a similar definition of size, along with novel property components. What constitutes inventions vs fundamental principles of biology or physics that should not be patented?

PTO is not the only agency dealing with nanotech. The Food and Drug Administration (FDA) has approved such devices as particles for imaging, wound dressing, dental restoratives, makeup, and sunscreen. Indeed, the FDA regulation of nanotechnology may have implications for PTO. Generally, nanotechnology in the FDA sphere is not looked upon as novel. An analysis of the current intellectual property landscape and comparisons with other technologies suggest that we can expect some contentious debates and litigation arising from the development and patenting of nanotechnologies. In the near future, the difficulty of decision making will be compounded by the unfamiliarity of PTO and the courts with this new science.

Public communications are critical. What gets communicated and what the public hears are two nonidentical things. Social science research indicates that public opinion is formed in complex and subtle ways, creating important implications for successful public outreach and communication.

Synthetic Biology

One current definition of synthetic biology is "the design and construction of new biological parts, devices, and systems and the redesign of existing natural biological systems for useful purposes" (Drew Endy, Massachusetts Institute of Technology, www.syntheticbiology.org). Scientists learn about the natural world by poking, prodding, and testing by building; as true as this is for mechanical devices, so too is it true as we seek to understand living systems. Scientists can go from information and raw materials—DNA bases—to compile a physical piece of DNA that then allows them to determine the potential "parts list" for living cells and make them. Can we as a society accept responsibility for the widespread and direct manipulation of genetic information and material? Some emerging themes include the following:

As synthetic biology advances, we can predict that innumerable legally and intellectually fascinating issues will arise for the courts. A court, however, does not shape law as much as it interprets law in the context of the case before it. This means that the court is always behind the social curve. It also means that scientists—who have a duty to be educators from their laboratory benches, an obligation that well exceeds the needs of individual cases—must participate in societal activities. Their expertise obliges investigators to think seriously about these issues and engage in the public discourse. Without such engagement, we will not have societal understanding or, concomitantly, good laws and regulations applicable to the issue.

Possible Response Models

What should the Office of Science do to establish and inculcate thinking about societal implications in these programs? A variety of possible response models were discussed, among them the following.

"Bedside Consult": A program at Stanford based loosely on the idea of the bedside consultation service used in hospitals. Its key features are that it is proactive, allowing researchers to raise issues before the fact; integrative; anticipatory; and educational in the sense that it educates researchers and consultants.

Asilomar Model: A major cross-disciplinary workshop of relevant scientists and others that explores an issue and determines a short-term policy (e.g., a moratorium) to get a community to coalesce around a path forward.

ELSI Model: Based on a granting program, establishes and cultivates a "bottom-up" capacity in a field by building a stable community of researchers who can take on these issues as a career. They also would stand ready to respond to urgent questions as they came along but would be a reliable resource on which society (including researchers) could draw.

Conference Model: Brings together recognized and up-and-coming experts in a field to discuss timely and familiar topics, making sure to present divergent views to encourage ample discourse and debate. Model also uses conferences that combine a diverse mix of practitioners, academics, poets, media, and artists to talk about topics, issues, or works that take them more or less outside their usual areas.

Regulation: Has four attributes of special importance.

- Nanoscience and technologies often differ in kind rather than degree from their antecedent technologies, making regulation challenging when using established vehicles and possibly requiring development of new approaches.
- Nanotechnologies will arise from science in progress, meaning that decisions will be required before a full understanding of risks is available and may need new approaches to regulatory decision making in the absence of adequate bodies of data.
- Nanotechnologies present special challenges and thus special fears (whether grounded in reality or not) and, as a result, pressures for precaution may increase, with less willingness to compromise or experiment in sensitive areas.
- Nanotechnologies may present significant external costs that are hard to anticipate. When the problems are more complex and the science less clear, choices are less obvious and reliance on values grows. When science is weakest, the regulatory system is forced to place greater reliance on value systems.

What the DOE ELSI Program aims to do next includes defining how studying societal implications can benefit the science DOE supports; making the case to DOE-supported scientists that they need to take studies of societal implications seriously because they are beneficial to science and society (not inhibitions on scientific progress); looking at issues down the road (since ES&H are being looked at already); inviting peer-reviewable studies of the implications of societal issues, while linking these to the ongoing science in tangible ways; building a collaborative environment among scientists and those studying societal implications; and experimenting more with less-conventional funding mechanisms. Program operating principles must include that scientists are well-served by initiating and being involved in discussions of the societal implications of their work; discussions should not be limited to human risks, exploring environmental risks as well; portrayal of benefits should be realistic (i.e., exaggeration will not help to generate trust); and the biggest lesson is that the social context is always changing, and scientists need to adapt along with it in their discussions of societal implications.

This ISIS workshop has resulted in one Request for Applications (RFA) already (www.science.doe.gov/grants/FAPN07-16.html) on "Ethical, Legal, and Societal Implications (ELSI) of Research on Alternative Bioenergy Technologies, Synthetic Genomics, or Nanotechnologies" that will begin funding new research in Fiscal Year 2007. This RFA is expected to recur in subsequent years to sustain and support DOE's interest in conducting advanced explorations of the societal implications of its research activities.

Agenda

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Workshop on Integrating Societal Implications into Science*

May 1–2, 2006

Monday, May 1

Welcome, Introduction of Participants, Logistics, Housekeeping

Daniel Drell (DOE Office of Biological and Environmental Research)

ISIS stands for Integrating Societal Implications into Science and is intended to be broader than ELSI (Ethical, Legal, and Social Issues), the long-running program from which we want it to evolve. The explicit intention is to interweave thinking about scientific activities and their potential societal implications to the maximum extent possible. We want to break down the distinctions between practitioners of synthetic biology and nanoscience and those exploring societal implications. In fact, they can be the same people. I make an assumption here: It helps all of us, including the scientists and the science, to look at the societal implications ahead of time. This isn't just a matter of good public relations (PR) or political shielding (though those are relevant); my postulate is that looking at the societal consequences can actually benefit the science in direct ways. Not an easy proposition to demonstrate. Can we make the case for "ELSI thinking" in a way that appeals to and convinces the scientists? I don't believe we have really tried in the past.

To get started, we want to explore the intermediate-range "issue spaces" for nanoscience and synthetic biology. There's been a National Nanoscience Initiative for a couple of years now, with many Federal agency participants. A major effort, principally funded through the National Science Foundation (NSF), is looking at health and safety issues and, for the purposes of this workshop, we'll take it as a given that this is being well covered and that we don't need to repeat what they are already doing.

Workshop Aims

- Explore the intermediate-range issue space for nanoscience.
- Explore the intermediate-range issue space for synthetic biology.
- Discuss the nature of a response capability for future challenges the Office of Science might face.

What can DOE do to have a capacity to address any societal issues that may arise within the scope of the programs it supports? There's a page and a half of language in the National Nanoscience Initiative that requires us to look at these issues.

Desired Outcomes

A list of topics from which the Office of Science will select a modest research program and a plan (subject to evolution within the Office of Science) for a response capability should the need arise to address and respond to challenges arising from our programs. We will start with nanoscience and synthetic biology, not because those are the only issues, but because they have received a lot of public attention recently.

*Written from best notes available by Denise Casey (Genome Management Information System, Oak Ridge National Laboratory).

Thinking About Nanoscience

What is Nanoscience, and What is Its Promise?

A Primer for the Nonscientist

Mark Alper (LBNL)

Nanoscience is too broad and diverse a field to discuss as a monolith. It is not a single entity. It's like saying, "What are plastics?" There's a unifying theme in that plastics are various organic compounds produced by polymerization, but there is a very large number of types.

So, what is nanoscience? The unifying theme is that it involves objects with at least one dimension on the order of 1 to 100 nanometers. Is it a crystal, a rod, or a more complex structure? Is it a hollow sphere, a tube, a nanowire? A lithographic feature for computer chip design? A protein (e.g., a glycerol channel that transports things in and out of cells)? An inorganic crystal linked to a protein inserted in a cell to identify different structures in a cell? Is it part of a molecular machine? Are there rules we can apply to generalize this?

Properties of Nanostructures

1. Nano is small—1/100,000 the width of a human hair. A billion dollars is to one dollar as a meter is to a nanometer. DNA is 2 nm wide.

2. Nano is not new. Examples:

- Soot from combustion and incineration for energy generation
- Diesel engine exhaust
- Carbon black used in tires and paint
- Titanium dioxide used in paints
- Synthetic chemistry (dealing with nanosized structures for the last 150 to 200 years)
- Biology

3. The properties of nanostructures vary with their size. This is a controversial definition; for many it's not really nano unless properties do vary with size. An iceberg melts at the same temp as an ice cube, but a 2-nm semiconductor nanocrystal melts at a far lower temp than a 6-nm crystal.

- A large object is the same color as a small piece of it, but not at the nanoscale. Crystals are green at 2 nm, yellow at 5 nm, and red at 6 nm. This property can be put to use.
- A catalyst is a material that accelerates a chemical reaction. Catalytic activity can vary with particle size.

4. Nano is where biology meets nonbiology.

- Crystals that we can now make: a synthetic glycerol channel is 5 nm, and a cadmium selenite CdSe nanocrystal is 5 nm.
- Nanobiology can be both an application of nanoscience materials to an organism for biomedical purposes and an application of biology outside an organism to use biological structures as physical structures. The driving force is that we can now control large biological structures like proteins and small physical structures like crystals when they are at the same size scale.

5. Nanomaterials are very sensitive to changes in structures. Examples follow.

- Thalidomide is teratogenic (causes birth defects). Two forms of Thalidomide are known, one (the S optical isomer) that is teratogenic, the other (the R optical isomer) that is a sedative and a good drug for cancer therapies and leprosy. The only difference is a subtle one—they are mirror images.

- Consider a nanotube made of carbon. It's like rolling a chain link fence into a tube. You can be careful and have it aligned so hexagons match up. Or alter it a little bit and have an angle—the atoms are still the same, molecular weight and size are same, but structural difference confers very different properties. When the hexagons match, it is conducting, and when there is a mismatch, it is a semiconductor.
- Biology examples: Biochemical manipulations such as the addition of carbons to a structure; synthesis of cholesterol, testosterone, estradiol, and other biologicals. Very similar biochemical structures can lead to very different properties.
- Sugar-coated nanotubes: Carbohydrate groups (sugars) are found on cell surfaces. Mucin mimic polymers can be used as biocompatible coatings for carbon nanotubes with drastic differences in properties. Certain mucin mimics will solubilize carbon nanotubes. When coated cells in a culture are looked at over time, the cells growing on mucin-coated nanotubes grew well. Unmodified carbon nanotubes inhibited cell growth.

Examples of Nanoscience Today

- **Scanning tunneling microscopy.** Most STMs are designed with electronics such that the tip can focus on a single atom. It is possible to look at a surface and find where individual atoms are and even to manipulate them. Two individual nickel atoms can be pushed together and become a nickel molecule. A classic buckyball (C_{60}) sitting on a silver surface with K atoms can be manipulated with a scanning tunneling microscope probe to capture individual K atoms, resembling Pacman. In the process, the C_{60} picks up an electron and changes its properties. There's a lot of experience with this in semiconductor industry, adding electrons to buckeyballs to change their properties. If they hit a defect in the surface they lose the electron, which can be informative about the surface.
- **Mixing of biology and inorganics.** An example is a self-assembled dendrimer-DNA hybrid. This mixes DNA with groups that are optically active. The nature and wavelength of the emitted light (the optical activity) depend on the distance between the dendrimer-DNA hybrids; they have a variety of applications in probing molecular interactions and processes within a cell.
- **Putting nanostructures together to make a more complex structure.** Lithographically directed nanofluidic assembly permits control of the relationship and spacing of individual nanocrystals to enable synthesis of more complicated 3-D structures.
- **A multiwalled carbon nanotube can telescope in and out with no evident wear or fatigue and extremely low amounts of friction.** These may constitute ultralow friction linear bearings, with many potential applications.
- **There are a lot of theories now in nanoscience to predict experimental data.** Can we build electronic circuits? We are exploring the limits of nanoelectronics with theory: single molecule electrical junctions. We want to understand the flow of electricity through single hydrogen molecules bridging palladium point contacts. We can predict theoretically how much current should flow through in a structure like this. If experimentally confirmed, perhaps we can replace conventional electronics someday.
- **Solar cells.** Two issues here are efficiency and cost. Can we construct hybrid solar cells using nanorods and nanowires to capture solar energy and turn it into electricity? Preliminary evidence suggests that such solar nanocells can be efficient. Nanotubes of titanium dioxide can be modified to respond to visible light for the purpose of splitting water for hydrogen generation.
- **Smallest lasers—nanolasers of ZnO (zinc oxide).** Ultraviolet nanolasers have been manufactured. We can start to put them into electronic devices that are very small and, perhaps in the near future, power computers with them. We use wires with current going through them now, but what about nanowires with light going through? Nanoribbons can be used to steer light.
- **Another example—windshields that don't fog up**. Coated with nanosilicon, there are applications for glass coatings.
- **Clothing.** Liquid beads up on fabrics. Eddie Bauer nanotex pants have nanotubes embedded in them.

A major application area for nanoscience is medicine, for example, diagnosis and therapy in biomedical imaging. Different sizes (and colors) of crystals can be used to bind to specific structures in cells. Can we take these

crystals that are hollow, put drugs in and use to search (i.e., tumor cells) and deliver drugs? Nanocrystals will continue to light up for a longer time and follow diagnosis and therapy over a long time. Companies exist today that have been built on this. Q-dot nanocrystals, the National Cancer Institute Alliance for Nanotechnology. See website at http://nano.cancer.gov/index.asp. Such technologies could have a great potential impact on cancer. Nanotech in postgenomic era promises to transform oncology and other fields of medicine.

A key challenge is self-assembly, because you can't pick these structures up and move them from one place to another. We need to develop structures that have desired properties and can self-assemble into desired higher-order structures. All of us, as individual organisms, are self-assembled because all the molecules in our body have properties that, individually or perhaps more commonly in concert with other molecules, express properties that we need for functioning. This is a challenge in nanoscience: can we emulate what biomolecules do naturally?

To summarize, nanoscience is not one thing but will be many. It's a very broad (and active) field, with all kinds of applications and structures being worked on, including structures that change properties as a function of size. More research is needed to allow us to predict behaviors. We need to be careful when talking about nanoscience that we focus on exactly what mean and the reality of the science as we know it.

Societal Impacts of Nanotechnology

How DOE Might Respond to Regulatory Challenges

Charles Rubin (Duquesne U.)

Efforts to anticipate the impact of nanotechnology are in their infancy, but a standard model is already developing. It starts with promises for dazzling possibilities in health, various products, and energy - a strong motivation behind the hopes for progress, whether it means using nano for improvements to current systems for more efficiency or developing novel systems. But if nano promises to make us healthier and wealthier, can we also be wise in deploying these new technologies? How does such a quest for wisdom fit into the DOE core mission? Answers to these questions require acknowledging some pitfalls in the standard model used to explore the impacts of nanotech.

1. The first maxim of wisdom in the standard model is to be skeptical and avoid hype about what the impact of nanotech will be Fair enough, but what exactly are we to be skeptical about when, despite some signs of convergence, there is still debate over what forms of nanostructures, whether nanates (new materials) or nanites (new replicators), are likely or even possible? Anticipating societal consequences means foreseeing what is even possible, which is no easy job in itself.

2. The standard model also says that whatever happens, there will be risks as well as benefits. Three big issues already in play here are safety, efficacy, and equity. In each case, a focus on risks and benefits is really more a starting point for contention than a method of projection. With safety, some will say we should invoke the precautionary principle, while others will claim that the approach will sacrifice huge benefits. Discussions of efficacy led to questions about who will ensure that nanotech works as promised. How much will be done by transparency and responsiveness vs governmental regulatory efforts? Will national efforts be enough, given the international interest in nanotech?

3. When we speak of equity we assume we know how rewards of nanotechnology should be distributed. But another maxim of the standard model is that nanotechnology will produce winners (new jobs and fields) and losers (occupations and products that will pass into oblivion). New choices and new professions will require new norms of behavior. Some will welcome this change and the new technologies; others, seeing these as problematic from their point of view, will resist them along with the technology.

The standard model seems to be telling us little more than to expect a nanotechnology regulatory environment that will be as contentious as any other. Yet can a technology that promises to be revolutionary be treated in a

business-as-usual framework? On the other hand, can we apply unprecedented scrutiny and drive development to countries that are less scrupulous in their concerns?

The standard model operates at a high level of generality. Is that the best we can do? Apparently so, since it also reminds us that serendipities will have their place in nanotech development and therefore our foresight, at best, will be limited. Such uncertainty has its uses, suggesting that the likely societal outcome will be neither Utopia nor oblivion. Nanotech will neither assault the environment and kill us all, nor will it open a door to prosperity for everyone. To think otherwise, the standard model says, is to exhibit tunnel vision that puts too much weight on technological change in comparison with social, political and economic constraints. But this thought runs up against another maxim: even small technological changes can have cascading consequences for social, political and economic systems.

Looking critically at the standard model suggests why we're not good at anticipating societal consequences. When faced with technology that has revolutionary implications, the extant systems we have for our already limited understanding the present don't help much with understanding the future. Even if we could better predict, what could we do with control? Defense Advanced Research Projects Agency (called DARPA) creators of the net, I'm guessing, didn't foresee porn, spam, and gambling as uses of the Internet—and if they had, what would they have done?

So why try to predict at all? First, because even in the face of our limitations, that's what modern science is all about - prediction and control. Second, because we have a professional sense of interest or obligation. Researchers working at the technological cutting edge may want to act responsibly. Social scientists have tools they are itching to use to study social change. There are reasonable motives, but there are problems associated with them. Even when these efforts are interdisciplinary, they produce groups of people who talk to each other in a subspecialty language they create. When that happens, the measure of success is less accurate foresight than the development of conferences, journals, grantsmanship, and a chance to lament that the real world doesn't pay attention to what they're saying.

The last prevalent reason for trying to anticipate impacts is that it's profitable to be at the cutting edge to produce a product or promote a cause. But that hardly leads to disinterested foresight.

To say that our efforts are imperfect is to say they are human efforts. The imperfections I've talked about highlight a common characteristic: conventional predictions focus on facts, not values. When values enter in they are either treated as givens (survey research) or adopted from the fashionable the normative discourse of the moment (e.g., nanotech is good for sustainable development). In contrast, in the book *Diamond Age*, Stevenson points to the right, essentially normative question we should be posing in relationship to the future of nanotechnology: In it, he suggests that as our power over nature increases, what can be done is secondary to the question of what should be done.

As a mission-driven agency, DOE naturally wants to know what can be done. But a fact focus will not be enough to deal with the regulatory conflicts nanotechnology will create. DOE needs to deal with fundamental value questions like, why will the world be better off with nanotechnology than without it? Political disputes are between differing visions of how the world ought to be. A foresight that devalues values doesn't engage this debate and will be not as useful.

Two suggestions to move the discussion forward:

1. Understand the usefulness of scenario building for foresight. It's a way to develop a set of assumptions in a disciplined way to allow questions on what we expect and what we want. Good science fiction provides these scenarios ready made. It's what advocates and critics are already doing when they project imaginary wonderfuls and horribles. The key is to get to the normative assumptions behind their projections.

2. Don't slight prudence. When the focus is on technology it's all too easy to forget the people who will be using it, and start thinking they can be manipulated like things. If people can't be manipulated as readily as things can be, then expectations about the future will be flawed. If people can be manipulated, there is still a net loss of human dignity as a result. To be sure, that nanotechnology enhances human life, then the old question of what a good life is can't be avoided.

What is on the Horizon?

Tom Vogt (University of South Carolina)

My comments will focus on materials, energy, medicine, healthcare, and human development. These impacts cover different time scales, and all these areas are intertwined with environmental science. For example, nanoscience will be a boon to bioremediation in the next few years.

- Materials: short term, low impact.
- Energy: mid term, medium impact
- Medicine: long term, high impact. Potential of "the future ain't what it used to be."
- Nanomaterials: passive and some active nanostructures
  - Dispersed and contact nanomaterials (aerosols, colloids)
  - Products containing nanomaterials (composites, ceramics)

Is the current regulatory framework sufficient? I believe there are tremendous problems with the current regulatory framework: it simply isn't designed for nanomaterials. The Occupational Safety and Health Administration (OSHA), for example, will probably regulate nanomaterials as particulates (nuisance dust) but not under other possibly applicable regulations. PPE is currently not certified for nanoparticles between 30 and 70 nm. Material Safety Datasheets are inadequate. General duty clause applies only to recognized hazards, not novel ones.

Toxic Substances Control Act (TSCA)

- No health data required on premanufacturing notification
- Would a nanostructure of a known molecule be considered a new chemical?
- Cosmetics, fuel, and food additives are excluded from TSCA

There's a wide danger zone here that may stimulate labels such as "New Asbestos" and "No Nano" [like "No genetically modified organisms (GMOs)"].

We are setting ourselves up for a dangerous zone, particularly after what happened in Germany recently with "Magic Nano" bathroom spray cleaner that induced respiratory problems in 45 people, leading to its recall by the government.

What needs to be done?

- Updates of the regulatory framework to remediate obvious shortfalls
- An increase in nanoscience risk research. The target should be more than $100 million; currently it's $38.5 million in 2006 in National Nanotechnology Initiative (NNI) budget
- Rapid development of voluntary standards and best practices, global standards about risk analysis and assessment

Legal regulation of nanotechnology?

- Can legal regulation coevolve with nanotechnology? May not be likely.
- Adverse events usually precede legal regulation (e.g., Megan's law, Patriot Act, Clean Water Act, Clean Air Act)

How do we regulate the unknown?

- Between laissez faire and a ban or moratorium. Need to understand how risk distribution, local restrictions, and regulatory processes work together to shepherd this technology

Why nanotech companies might not take legal precautions:

- Startups live in short time frames and need to recover return on investment.
- Venture capitalist firms are under capitalized and unable to cover insurance claims.

It's much easier to invent and produce nanoparticles in China—is that what we want to do?

My thoughts on ISIS/ELSI in energy

- **The drivers:** Energy independence and global security, global warming
- **The challenge:** 30 terawatts for over 10 billion people by 2050 at the lowest possible CO_2 footprint.
- **Expectations:** Nanoscience will provide revolutionary breakthroughs in energy-related science and technology and in particular a hydrogen economy (production, storage and use), utilization of solar energy, lighting, batteries and ultracapacitators.

How do we manage uncritical euphoria and expectations?

How do we balance conflicting values between environment, economics, and societal implications? Energy scenarios need to be explored.

If you want to stabilize greenhouse gas concentrations, there are a few options. Do we need nuclear energy? What role will fusion play? If we want to do this, we need to have an energy transition based on

- Revolutionary, not incremental, science and technology
- Cultural change

Sobering historical lessons about energy transitions:

- Not implemented—consensual
- There are winners and losers
- Change the social structure

Look at the transition from wood to coal (Wilkinson book: *Poverty and Progress*)

- Driver: Population growth that led to a resource crisis—not enough wood.
- Easy coal mining began, but:
  - Higher production costs
  - No distribution network
  - Increased pollution (chimneys appeared)

Initial change resulted in diminishing returns and decline of the general welfare. Coal was depleted, localities ran into groundwater problems, the cost of coal rose, and the steam engine developed. All helped lead to the Industrial Revolution and coal-based economy—this was bootstrapped; they didn't have all this technology in place. So for an energy transition we see increased returns and increased welfare from initial declining returns and reduced welfare. Transition activation barrier was overcome.

Now we have a vision of a hydrogen economy with no carbon base. Will need to have nuclear or solar, delivery issues, storage issues, see how it can be used for utilities, commercial and residential, transportation needs. Hydrogen today is from carbon-based sources: gas, oil, coal. In the short term we will continue to produce H but have to sequester the CO_2 produced.

Two Extreme Scenarios

Reluctant Change Scenario

Oil and gas price increases makes "clean coal technology" competitive.

- Coal is most abundant fossil fuel on earth.

- Over 200 years of supply available.
- Energy independence achievable in a short period.

Use nanocatalysts for steam reforming and water gas shift reaction; hydrogen combustion, gas turbines, ice, fuel cells (nanocatalysis); burn ourselves to a hydrogen economy.

Reluctant energy transition issues:

- Cost benefit analysis: how clean is enough (tech and political)?
- Continued tradeoffs between economics and environmental burden
- CO_2 sequestration at centralized facilities
- Initial urban advantage over rural areas (distribution network)
- Over time, lower energy density sources such as wind, hydro, wave
- Overall impact: gradual change; low level of disruption.

Radical Energy Transition Scenario

- Fast and aggressive implement of renewables
- Existing energy infrastructure becomes rapidly obsolete
- Renewables production is local, dispersed, and rural
- Decentralization of society (general to personal electric, rural renaissance in a knowledge-based society
- Urban decay—a new rustbelt?
- Significant workforce shifts

Truth will be not in extremes but somewhere in between. Scenarios need to be explored in more detail. We need an ISIS/ELSI and science road map. Developing a technology road map without ISIS/ELSI interactions involved is not good. You need to combine these to mediate conflicts seen on horizon and have a frank discussion. High societal impact: medicine, healthcare, and human development. The value and understanding of life and death will change radically. Significant segment of society will challenge scientific research projects and directions

Predictable "Biopolitical Battlegrounds"

- Right to life—abortion, stem cells, brain death (Schiavo)
- Control of reproduction (contraception, abortion, fertility, genetic testing, germline gene therapies, cloning)
- From treating disabilities to human enhancement: cochlear implants, prosthetic eye, brain chips, gene therapies, cosmetic procedures (radical makeover)
- Extending life—from treatments for aging-related diseases to antiaging drugs
- Control of brain: Ritalin and Prozac, brain chips, and psychoactive drugs

Societal implications

After defeating cardiovascular disease and cancer, medicine will be the science of aging.

- Life spans over 100
- Inequity in developing and developed world
- Fertility beyond 50s and 60s—kids as retirement projects?
- Redefinition of human life cycle from cradle to grave
- New generation conflicts

Is aging a disease or part of the human condition?

- Values about life will be radically challenged by nanotech advances.
- Plants, viruses, and microbes will be used as chemical reactors.
- The distinction between animals, plants, and machines will blur—molecular farming, tobacco fields to create industrial products like rubber.
- Genetic engineering will be used to design animals and plants.
- Opening Pandora's Box and engineering humans or humanoids
- A fusion of man and machine
- From medical and cosmetic enhancement to military applications
- Sensors, cochlear implants, retinal chips for the blind, neurofeedback using brain chips
- Military interest to expand acoustical and electromagnetic spectrum "soldiers" can detect
- Effective communication between man and machine
- NBIC (nanobiotech-artificial intelligence-cognitive science) convergence
- Nanomedicine and cognitive science. Brain science will become a frontier of research
- Also, the potential for sentience in computers
- Intelligence without life?
- Awareness

What about the far-reaching consequences? The development of active nanostructures and nanosystems and hybrid structures raises questions about human risks.

Morality and use of nanotech:

- New moral debates: possibilities for stimulating the brain like psychoactive drugs, could provide on demand sexual pleasure, modify body with ease and enhance performance, change genetic coding of future children
- Who should be allowed to use them?
- Who should determine the regulation of these devices? Public, Congress, judges, individuals, scientists?

ISIS/ELSI will influence the evolution of science as an epistemic institution:

- Will challenge the nonethics stance—utility is a moral concept
- Engage in public discourse (participate or perish)
- Evolution from privileged to distinct epistemology

Nanoscience is the first full embodiment of post-academic or mode2 science.

- Will shape how technology is implemented.

The Intellectual Property (IP) Landscape

Lori Andrews (Chicago-Kent College of Law)

NNI reports that the federal government is providing $1.3 billion to nanotech efforts this year. The legislative language suggests some of that funding should be spent on societal implications research. Federal funds are being mirrored by state investment—about $400 million total last year. At least 19 states have enacted legislation involving the promotion or funding of nanotechnology, including direct funding, tax incentives, and educational grants. Already at least 1200 startups have launched to capitalize on this investment. But development of nanotechnology–and its contributions to people's lives and the economy–will be influenced extensively by the rules of intellectual property.

Although the underlying goal of the United States Patent and Trademark Office (PTO) is to encourage innovation, sometimes it hinders it, as when the PTO refuses to grant a patent when it is appropriate or grants a patent when it is inappropriate. PTO now is trying to figure out what "nano" is. The definition from NNI requires a size range of 1 to 100 nm, with unique phenomena that enable novel applications. PTO uses a similar definition with size and novel property components. State laws have definitions as well. Some focus on size and new properties, while others just require that a device be small. In addition, "nano" is being used as a marketing term (e.g., the Apple "iPod nano").

There is a rush to patent things with "nano" in the name. How PTO responds will have important implications for future research, development, and innovation. The U.S. Constitution views innovation highly. We encourage innovation by awarding patent invention rights for 20 years, essentially granting a monopoly to the creator. This is an incentive to invent. Under the federal patent statues, 35 U.S.C. §101 *et seq*., certain requirements must be met: inventions must be novel, nonobvious, and useful. The inventor must also provide a written description of the invention to enable someone skilled in the art to make and use the invention.

The system is a three-way give-and-take among Congress, PTO, and the courts. PTO grants patents, and Congress and the courts winnow them back. Example: Samuel Morse convinced PTO to give him all uses of electromagnetic waves to write at a distance. The U.S. Supreme Court disagreed, holding that the patent applied only to his invention—the telegraph. Another example: in the mid-90s surgeons started to patent their surgical methods. The American Medical Association went to Congress and said this practice was not good for medicine or for research. Congress amended the law, and now doctors can use patented medical procedures and not pay a royalty. Nanotechnology could raise concerns similar to both of these situations.

Parallels can be drawn between the emerging nanotechnology industry and the established biotechnology industry. In *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), the U.S. Supreme Court reiterated that laws of nature, physical phenomena, and abstract ideas are not patentable. This is necessary so future innovations can be based on basic scientific ideas.

However, there is increasing concern that PTO has contravened Supreme Court precedent that laws of nature are not patentable. In *Laboratory Corporation of America v. Metabolite Laboratories, Inc.,* 548 U.S., 2006 U.S. _, Lexis 4893 (2006), researchers developed a test for the level of the amino acid derivative homocysteine in the body after finding that a high level of homocysteine correlated with vitamin B deficiency. These researchers received a patent on their test, including a claim for rights over any other tests that used the basic biological fact that high homocysteine is correlated with vitamin B deficiency. LabCorp acquired this patent and marketed the test. A better test for homocysteine existed, and it was not a patent infringement to use it, but the Federal Circuit (the appellate court that deals with patent issues) held that it induced infringement of the patent for a laboratory to publish the correlation and that doctors directly infringed the patent by thinking about the relationship of test results to vitamin deficiency. So in theory, doctors can use alternative tests for homocysteine but can't think about what the results mean for patients. In oral argument in the U.S. Supreme Court in March 2006, the justices pointed to their 154-year precedent that patents are not allowed on laws of nature, expressing concern that the patent contained unpatentable subject matter. The case was ultimately dismissed because the U.S. Supreme Court found the question had not been properly raised below, but it is evident that the Supreme Court is troubled by the patents that PTO has granted.

In July 2006, PTO solicited input on its guidelines used to assess subject matter eligibility, including a determination of when a patent claim contained a law of nature. In the nanotechnology sphere, questions arise as to whether certain nanoprocesses are actually fundamental principles of biology or physics and thus should not be patented. The prospect for developing technologies based on nanoscience, such as solar panels with nanowires, is exciting. However, the first patent on such an invention may impede future inventions of better nanowires to use for solar purposes.

PTO is not the only agency dealing with nanotech. The Food and Drug Administration (FDA) has approved devices such as particles for imaging, wound dressing, dental restoratives, makeup, and sunscreen. The FDA regulation of technology in these areas may have implications for PTO. Generally, nanotechnology in the FDA sphere is not looked at as novel. For example, in 1999 in over-the-counter sunscreens, FDA addressed whether

nanoparticles were a new product. It determined that sunscreen manufacturers didn't need to seek additional approval for the nano form of previously known products. This shows short-sightedness, given the new properties nanostructures could have. It also causes concern about whether nanoinventions with novel properties will be viewed as unpatentable by PTO if the FDA has said they are not novel for FDA purposes.

Another patent issue is strict liability. Having the intent to infringe is not relevant in patent law; you may infringe a patent without meaning to. In the case of nanotech, for example, someone could sneeze and pass on a patented medical nanotechnology to another. The other person might not benefit or could even be harmed by the nanoinvention but still could be seen as infringing the patent and thus be required to pay royalties.

Also, inventions may be patented in some countries and not others. What if Canada produces or sells a less expensive version of a nanotechnology product or medical device? If people travel from the United States to Canada to take advantage of the lower cost, a U.S. company may sue people returning to the country for patent infringement.

In addition to legal issues, PTO faces many practical issues. A look at the DOE website (http://www.science.doe.gov/Sub/Newsroom/News_Releases/DOE-SC/2006/nano/index.htm) shows the span of nanotech across many different disciplines. PTO is not organized to deal with technologies across boundaries; it has eight technology specialization centers. It doesn't have clear mechanisms for assessing inventions spanning multiple centers. So what will it do? It hasn't done well with new technologies in the past. For example, when the U.S. Supreme Court said patents were permissible for computer programs, PTO started granting overly broad claims because the examiners weren't trained. With gene patents, we found that 38 % of patent claims granted by PTO did not meet the legal requirements of the Patent Act. Nanotech is a whole new field of technology—is PTO ready to deal with it? Nano patent claims are scattered across PTO with no dedicated specialists or art units. PTO examiners may not be diligently researching prior art; in addition, they have financial incentives to grant patents. A huge number of patents already have been granted on nanotech, for example, over 1000 for "nanoparticles" alone, and we are beginning to see the first litigation arising from disputes over ownership. Overly broad patents stifle developing technology and waste public resources through litigation.

In terms of other issues, because of the large number of nanopatents and their broad scope of coverage, you need broad cost-efficient licensing. Patents, however, are distributed asymmetrically in this field and there is less of a rationale for voluntary cross licensing, which means the licenses might not be cost efficient. A disproportionate number of granted nanopatents are held by universities. This is an issue because universities tend to license their patent rights exclusively, rather than trade them or license them nonexclusively. Exclusive licensing often leads to expensive end products. As an example, consider that Myriad, the company that owns the BRCA gene patent test, charges about $3000 for its breast cancer test, while other genetic tests are about $100.

Potential solutions include nonexclusive licensing, march-in rights under the Bayh-Dole Act, patent pools, or compulsory licenses. An analysis of the current intellectual property landscape and comparisons with other technologies suggests that we can expect some contentious debates and court cases arising from the development and patenting of nanotechnologies, added to, in the near future, by the unfamiliarity of PTO and the courts with this new science. These debates and cases have the potential to impede research and stifle innovation.

Communication and Public Perceptions

Dietram Scheufele (University of Wisconsin)

We always end up saying that the public doesn't listen to us and that we need to do something. In my view, we haven't paid enough attention to social sciences that can inform us about what we communicate and what the public hears. The two are not the same.

Overview of my talk:

- There are several models of media effects: deficit models vs more recent models;
- What we know about public opinion;

- How it all fits together (i.e., how attitudes are formed and what it means for
- successful public outreach and communication);
- A few predictions.

Media affects models

1. The science literacy model assumes that the public has relatively low levels of information about science issues, that it has uninformed attitudes and opinions, and that it needs more information. I challenge this. People form opinions and attitudes based on more than information. In politics, it is accepted that most people don't vote based purely on information.

2. A more precise effects model assumes people learn from the mass media. Most people can't place candidates on issues, but the gap narrows as we go through debates. People make decisions about trust and take cues from the mass media in the same way they do from entertainment. Consider that very few of us have direct experience with labs to base our opinions about science on. Most people overestimate becoming a victim of crime because of TV.

Public opinion

There's a spirals-of-silence model that says that a lot of people form opinions based on what they think the majority thinks. For example, an organization called THONG (Topless Humans Organized for Natural Genetics) is opposed to developments in biotech and nanotech, saying that corporate America is trying to impose unsafe technologies on the public. This model says if people don't know much about an issue, then a vocal minority can create the predominating opinions. People tend to fall silent and this makes certain groups appear louder and more visible. Over time, this turns into the "majority" opinion because of the silence of others. One question to ask is, "Regardless of who you are going to vote for, whom do you think will win?" This turns about to be an excellent predictor of the winner. The spirals-of-silence model is critical for explaining movement against nuclear energy in Germany and the backlash against GMOs.

Framing is important in what we see happening now. This says that you can present the exact information as one group but if it's labeled differently it will evoke a different reaction. President Clinton changed the phrase from "gun control" to "gun safety." Suddenly the image evoked changes from a challenge to the Second Amendment and government regulations to pictures of kids getting killed. The language of the 21st Century is all about framing. The Republicans are good at this to get certain images across: conservation vs environmentalism. A 200-page memo on this continues to be very influential.

In common with all the above models is another model called the "cognitive miser." This holds that:

1. People know very little about most issues, including scientific issues.

2. There is a rationale for having a low level of information.

3. It doesn't make sense for most people to develop in-depth understanding of issues; there's too much information around.

4. As a result, they form attitudes on issues such as nanotech using heuristics or shortcuts.

Examples of such shortcuts include:

1. Personal predispositions (e.g., religion, ideology)

2. Cues from mass media (e.g., costs and benefits), which right now, is positive toward nanotech

3. Other affective and emotional responses (influences of majority opinions, trust in scientists)

The following are a few findings from a 2004 survey done with Bruce Lewenstein (Cornell). This was a national random digital-dialing survey of 700 people who were interviewed about nanotech. A lot of money was spent making callbacks to people who initially refused, so they could keep their survey nonresponse bias to a minimum. We asked about basic and specific knowledge on nanotech and its economic implications; we found that

people knew very little. We looked at perceptions of risks vs benefits. Respondents expressed a concern about the possibilities of a loss of privacy. For assessments of risks, we found no significant differences between aware and unaware respondents. For assessment of benefits, there was a consistent difference between these groups: the more aware people know and read more and are more optimistic (this would seem to agree with the deficit model that says all you need to do is supply more information to people). But we may be seeing the effect of current media coverage, which now is framed in positive fashion. The coverage is dominated by business and science writers like Rick Weiss (*Washington Post*) who wrote the first mainstream news article on "Magic Nano."

Since 2004 the percentage of risk articles in the United States has been fairly stable, but I predict nanotech coverage and spin will pick up. Some points:

1. At this time in the United States, there are mostly positive frames based on the economic and scientific potential of nanotech.

2. This will change.

Knowledge and awareness will increase. But mainstream media interest groups and policymakers will offer competing ways of framing and preserving the issue. Hard news and entertainment also will start offering competing frames, like Frankenfoods (GM foods). Some possible frames could be like those now emerging in Europe. Examples include a German article on "The Asbestos of Tomorrow?" and a different story with a more positive spin suggested by the use of the word "nanowissenschaft" (meaning nanoscience) instead of the word for nanotech, which carries Monsanto biotech baggage.

A few questions that we need to answer:

- What frames may trigger interpretive schema and perceptual lenses? People make decisions based on frames (e.g., Tony the Franken tiger).
- How will media coverage develop over time?
- How does media coverage influence audience perceptions?
- How can we use this knowledge to engage in successful information and outreach?

My project at Wisconsin is to collect public opinions using a series of surveys that match up to deliberative meetings at the Center for Nanotechnology in Society at Arizona State University. They already are beginning to track media content (e.g., frames used). They are used in an audience-focused approach that looks at information seeking and will do framing experiments using whyfiles.org@UW. They will use this as a test ground for presenting scientific information in the best ways. For more information, see: www.nanopublic.com.

PANEL DISCUSSION: What are the Key Issues?

Alper, Rubin, Vogt, Scheufele, and Andrews

Lori Andrews for Tom Vogt: She was with a scientist who stopped a nanoproject because he couldn't ensure the safety of the masks he used. What suggestions does he have about what first steps could be done? These tie into scrutiny of the research phase.

Tom Vogt: The most important thing is to use best practices in labs, to treat every new material as a potentially toxic substance. I teach my students this, making a culture of growing up in that, it's an educational component. One also needs to make sure that when materials are manufactured we have more control. Right now it's difficult to detect particles when they go below a critical size in labs or even in clean rooms in industry. There's an issue of developing the instrumentation to detect these particles. From a regulatory point of view it's important. In the limited number of labs that can do inhalation studies for biomedical implications, we are looking at how certain materials we use as protective equipment behave: what is the nanoparticle transmission rate? Providing research dollars for these types of studies is important.

Dan Drell: From the standpoint of PTO challenges, what happens when we get more into nanobio?

Lori Andrews: We need changes in the way patents are scrutinized. There needs to be a team approach and more work done to make prior art accessible. A key point is that applying for a patent isn't like applying for FDA approval; nobody checks if it works, so you have a piece in science like divining for people below rubble. You want the patent office to screen patents once they are granted to make sure claims are borne out. This might be helpful in the bio/genetics field, where they are now retracting early correlations between specific gene sequences and certain diseases, but those patents are still out there. They (PTO) need to scrutinize additional issues that are raised. PTO is entering the foray of bioethics without having the mechanisms to deal with it. For example, a patent holder of a gene patent is sayings no to prenatal screening. Others might differ about whether this is appropriate; it's a bioethics discussion and shouldn't be decided by PTO. PTO punted on this man-human hybrid claim but actually had no legal grounds to make the decision.

Charles Rubin: For the patent office to extend itself as Lori suggests may go beyond what they should be doing. Maybe burden of prior art should be on applicant.

Lori Andrews: Unlike in Europe, third parties can't challenge patents in the United States. It may not get reversed at the Supreme Court level; it may not even be challenged. You don't have enough representation outside the patent office. There are some gene patents on sequences that exist in nature; some scientists want to challenge this, but tech transfer offices at their universities tell them not to challenge it because they have patents on other genes that they want protected. Also, about prior art…are we willing to put the burden on the applicant?

Robert Friedman: Going back to Tom's point: researchers in his lab seem to have a healthy respect for the potential dangers, but is this common?

Tom Vogt: At the DOE lab where he worked, these issues were viewed seriously. Ultimately this could lead to loss of funding if you don't. At universities you are entrusted with undergrads and most people do take safety very seriously. Maybe one of the regulations we need to evolve is to make nano safety levels similar to bio-safety levels. There has been an evolution in setting up bioclean rooms; if the right people get together and are empowered, they could come up with standards. Whenever you build labs for the future, it's best to use more caution.

Doug Lowndes: Tom covered this well—the rigorousness of safety practices in DOE labs is true. We've built a new research building and no research with materials is done outside chemical hoods or vacuum chambers. We are also monitoring particulates between 100 nm and 1 micron, which is below clean-room level in the past. We're finding that there are filters available to completely remove the 100 nm to 1 micron range. We do these tests routinely. Below 100 nm, it is harder to detect, and we need research to develop these tools.

Mildred Cho: To Dietram Scheufele on the whyfiles project: Given what you said about the deficit model, what would be a good outcome of your project? There is an inherent problem that the whyfiles face, which is the same as with public models: there are wide knowledge gaps. Certain groups of society learn more efficiently than others. Certain segments–usually based on socioeconomic status–pick up more quickly.

Dietram Scheufele: The whyfiles project wants to address gaps and usage. People who go there are highly informed: the rich get richer. A question: How do we improve citizenship through the internet, through non-traditional forms of participation? Is there a way to deliver information that overcomes these inherent biases to use easily available information? U.S. Internet penetration is at >70% now. It offers the potential for an interactive setting without a public meeting. For example, with cancer patients, they can now seek out physicians and build the information environment they want in collaboration with scientists and doctors. My group anticipates a similar information environment; the whyfiles is less for delivering data than a way for the public to interact with scientists in a cost-efficient fashion that doesn't require a face-to-face meeting. All of this is in the developmental stage. Note that we are using the why files as a vehicle; we don't own this.

John Miller: Safety practices are not used everywhere; it's not the case in many universities. There's a wide spectrum.

Lori Andrews: In a project she knows of with novelists, geneticists, and artists, the artists (who sculpt) said they were prepared to use gloves but were looked down on by others as not macho. They were not appropriately concerned with safety.

Question to Dietram Scheufele about Frankenfoods: An official in Germany said he doesn't know why the United States is so nervous about having this ELSI nano discussion. You can explain the whole European GMO issue in economic terms–the value chain. The United States has been very slow to prime the pump of this conversation.

Dietram Scheufele: There are different factors in Europe and the United States. Some are economic–labeling of U.S. products closed markets. Press coverage of monarch butterfly studies (1996) said biotech (Bt) corn kills Monarch butterflies and Europe said it won't import Bt corn. Opposition was high in Europe, continues not to be high on the radar of the U.S. public. Some reasons:

- A two-party system doesn't lend itself to push certain issues. It's also related to issues that the Green party in Germany pushed. They've gone from obscurity to Joseph Fischer being the foreign minister. He was photographed beating a policeman in the 60s. There are reasons those views are important in Europe.
- Greenpeace had more success in Europe than in the United States by communicating with the public early on. Chaining yourself to a tree is important when you don't have a media outlet; now everyone in Europe can call a Greenpeace person. The key distinction is on the public opinion side; a lot of our research shows that heuristics carries over from one issue to next. If I don't like how Monsanto dealt with past issues, that will spill over to stem cells to other issues. It's a question of baseline trust.

Dave Bjornstad (ORNL): I have an intellectual property question. We're seeing a lot of business strategies being carried out—universities want to protect their patents, the Justice Department says you can have a patent pulled if it complements but not substitutes…do you see new things that will help to resolve this?

Lori Andews: [Defers to others who will be speaking later, but says the following] It will get more problematic. We're seeing multiple patents on the same technology. Carbon nanotubes have a couple dozen patents. We're going to see new players in this. Thinking and writing can violate a patent. System gets shaken up by new people coming in.

Amy Wolfe to Dietram Scheufele: In regard to changing opinions, how can that happen in terms of communication issues?

Dietram Scheufele: It depends on what you think is ethically acceptable. You could use a straight persuasive method. Advertising has spent a lot of time on this. There is a whole range of other tools. Most people don't have stable attitudes; they form new attitudes based on other issues. Why didn't Bush talk about abortion in his last campaign–he didn't want it on people's minds. Give them a bunch of other issues that influence what they are thinking about and it will prime them. You can use it in a persuasive way and don't make the Al Gore mistake. Gore had a long alphabetic list of issues on his Web site, while Bush had about 5. A lot of outreach programs are more Al Gore than Bush. We need to be more Bush outreach in terms of how we present this. People won't go through all that info. This is why he likes the why files–you can click down into it more if you want. Highlight the most important ones, and people can make decisions based on that. So, there is a range of different strategies; some are more persuasive and others more information based. It's not an equal plane. The moment a government agency engages in persuasive efforts, the more chance there will be of backlash. It's a fine line to not make the mistake of doing information overload that will not work and not be utterly persuasive.

Cate Alexander (NSF) comment for Dietram Scheufele: She's skeptical about correlating news coverage on technology with risk and benefit perception. So few newspapers have science reporters. Many studies look at the *Wall Street Journal, New York Times, Washington Post,* and *Science* magazine, but these don't reach a lot of people. On the other hand, stories that have legs are like Rick Weiss' "Nanomagic" story that are picked up by papers without science writers.

Dietram Scheufele: I agree. Early findings found the link between being more aware and more optimistic. If the stories do make it into other media outlets, they will be reframed. Think about local news–tying it to a

specific instance of something that happened to somebody. The frames will change to more of a conflict frame that will create a more critical outlook and people will take their cue from that. Understanding the process is critical, and scientists need to be talking to journalists. Scientists may feel they are being misrepresented, but it reflects the difference in understanding between journalists and scientists. Journalists reduce the complexity and frame. It's the opposite for scientists, who want to talk about the limitations of studies. There needs to be middle ground to communicate with journalists - and it's important for scientists to understand what it means to successfully communicate with local journalists.

Eric Juengst: What's the Nanomagic story?

Dietram Scheufele: A small company sold a bathroom sealer containing a nanotech component. It's a parallel to the Bt corn—it's supposed to help the environment. A pump spray was used first and it didn't do anything, so they switched to aerosol and sold it in a cheaper market. Around 100 people developed severe respiratory problems. Ministries in Germany got involved in testing. One of the assumptions is that the coating of aerosol interacted with a nanofluidic liquid and that produced problems. The media are jumping on this. Scientists say it has nothing to do with nano—not quite true because it interacted with the container. We try to brand as nano when it's in our favor and move away when its not. It's the first issue that happened with a nanoproduct. The European public makes decisions in a similar fashion to us. I haven't seen convincing data that there is a difference in knowledge.

Thinking About Synthetic Biology

What is Synthetic Biology, and What is its Promise?

Drew Endy (MIT)

I'll talk about synthetic biology, give some basic examples, and talk about why it's happening now and some societal issues I've encountered.

My definition of synthetic biology is on my web site (http://www.syntheticbiology.org):

- Design and construction of new biological parts, devices, and systems.
- Redesign of existing, natural biological systems for useful purposes.

There is lots of information on this website. I'll give two perspectives on why one would be interested in synthetic biology from the point of view of the biologist and the engineer. How we learn about science is basically by poking and prodding and "testing by building." From the point of view of an engineer, biology is technology.

Science Perspective

We learn about the natural world by poking and prodding, for example, working with retrotransposons. These elements make up 30% of human DNA by mass. They're simple things with two open reading frames (called ORFs) and an interesting life cycle. Their genetic material will be read out to make RNA and will be translated into proteins that interact with RNA molecules. The RNA gets back into the nucleus and DNA gets made from it and is reinserted somewhere else in the chromosome. They can copy themselves independently of chromosomal replication. The DNA content of these elements is nonrandom, very biased; for example, a prevalent mouse retrotransposon has about 40% adenine. A group at Johns Hopkins decided to resynthesize it and balance it out for bases and found its efficiency of going around the cycle was increased 200 times. This suggests that natural retrotransposons are under strong selective pressure to have a nonrandom distribution of base content and not to fill up the host genome.

Another basic example: We also learn by trying it out, testing by building. If you take apart your car, you still won't understand how it works until you can put it back together. So it is with our understanding of living systems. Here is a depiction of what we think the inside of a living cell looks like, but we don't really know. Here

is a billiard ball model of how a living cell behaves; you can figure out the math, but it's still not a picture of a living cell. So some physicists are starting to make measurements on how quickly proteins move around in the cell. They move about a factor of 10 slower than in a solution, but it still looks like random diffusion. Based on this, they have built a model of how they think proteins would interact with DNA. They built a ring oscillator, a little clock to turn DNA on and off; you can put bacterial DNA into the ring oscillator. When you do this, the bacterium controls the level of fluorescent protein—replicating cells, although not in phase. We can't explain the variation.

These examples describe why we want to build biological systems from the scientific perspective—to construct biological systems and see what happens.

Engineering Perspective

Now I'll talk about biology as a technology. Some examples: A group of students engineered bacteria to be responsive to light and change their color. They used this as, in a way, genetically encoded photographic film. They published a paper on this in November 2005 (Levskaya, A., et al. *Nature* **438**, 441–442, 2005). Two months ago, another group published a general programming language to fold DNA into whatever pattern we like in two dimensions. Nanoscale shapes and patterns were published.

Biology is good at making chemicals: Jay Keasling's group at LBNL is engineering bacteria to make artemisinic acid to treat malaria. We hope to make a lot of chemicals directly from engineered organisms. Green fuel—an MIT company is growing algae to reduce CO_2 emissions. At UCSF, a group is trying to engineer bacterial cells to respond to other bacteria and low-oxygen environments—for example, in tumors. They are trying to build engineered bacteria that can impose environmental controls on invasion of cancer cells. A recent paper from the Weiss lab at Princeton describes how they programmed spatial pattern formation using engineered cell-cell signaling. They have induced bacteria to produce a bull's eye pattern. Recently, scientists achieved the reconstruction of the 1918 influenza virus. Cloning of one organism's genome into the genome of another organism has been demonstrated (using the microbe *Bacillus subtilis*). The point is that it's possible to construct pieces of DNA 10 Mb long. So you can, in principle, construct any eukaryotic chromosome. The Fred Blattner group reported very recently that they had removed all the mobile genetic elements from an *E coli* genome. They then constructed a new version of *E. coli* that doesn't evolve as much; when you prepare DNA from it, it's much cleaner. My group reported in 2005 the "refactoring" of bacteriophage T7. Redesigning a genome will help make it easier to understand it.

Why is all this happening now?

Thirty years ago, modern biology began, based on recombinant DNA technology where scientists took two existing pieces of DNA and made a chimera. In the 1980s, polymerase chain reaction (called PCR) came along, and then automated DNA sequencing emerged. Synthetic biology makes good use of these three technologies but also is driven by three new, emerging foundational technologies: automation of DNA synthesis, standardization of biological parts, and abstraction (the definition of a useful hierarchy to begin to characterize biological complexity). These three additional new technologies are as important as the previous ones above.

Synthesis

Synthesis lets you go from information and raw materials—DNA bases—to compile a physical piece of DNA. There are productivity improvements in synthesis and sequencing. Synthesis is lagging behind sequencing, but it is increasing. (If you don't know what to synthesize, you won't do it). How does this impact the practice of biology? People spend about 50 % of their time to get the right DNA. Synthesis technologies drastically reduce this. Define the DNA we want and produce it. The way to think about synthesis is this: the living world is encoded by material (DNA that propagates); sequencing is the technology that gets us the information (sequences), and synthesis is the technology that lets us recompile that material. So we're decoupling the physical designs of organisms from their previous forms so we can get all sorts of things. This will impact our security landscape, the control of material transfer agreements, and ownership of materials.

Standardization Technology

In 1864 Will Sellers in the Franklin Institute developed a standard for screw threads and nuts. If you have a standard, you can get a replacement part. Today we want to know what is a standard for constructing DNA, for measuring a protein inside a cell, a standard for a genotype, what an operating system for a cell is—the answers will make engineering biological systems easier. My group now collects standard biological parts in a registry—it's the beginnings of a catalog of biological functions. A high-water mark has been a signaling genetic device that receives a signal in the form of a small modified sugar outside the cell and converts that to gene expression. It's a replicating biological system.

Abstraction Technology

The science of biology celebrates complexity. This is not good from an engineering standpoint because we're very good at engineering simple components but not at engineering complexity. We develop tools to manage the complexity. We have developed the beginnings of an abstraction hierarchy for programming in DNA. There are four levels:

- DNA
- Parts (e.g., F2620)
- Devices (does something we define)
- System (more complicated). Someone working at a system level doesn't need to know what DNA is made of.

This abstraction starts by paying attention to how information is exchanged across levels. We are trying to push this knowledge and know-how worldwide. To this end, we even published a comic strip about it.

What are the ELSI issues we've run into over last 5 years?

- Understanding and perception
- Ownership, sharing, and innovation
- Risk and security
- Community

Understanding and Perception

iGEM: international Genetic Engineering Machine competition. Teams of students (from around the country and the world) are making genetically engineered machines and showing them at MIT. Coverage on the MIT website shows a photo of smiling students with the caption "Synthetic biology students keep it real at the iGEM jamboree." MIT alumni are writing in and asking, What are you guys doing making biology students? Thus one misperception ("synthetic" students). Another example is a brochure from a Cambridge team. There's really tough security in the genetics and microbiology labs there, and the photos in the brochure show serious people well dressed in lab coats looking as though they are paying a lot of attention to safe practices--one way of "framing" this activity.

Lori Zoloth (San Francisco State University) has a list of a dozen issues she's presented to the community. Among them are DNA as the really real self; nature is fixed; nature is normative… . The question to propose here is the following: Can we as a society accept responsibility for the widespread and direct manipulation of genetic information and material?

Ownership Sharing and Innovation

We operate the standard biological parts registry, and it's free to the public. If we consider, for example, a programmable biofilm that's made up of five key genetic functions, how are genetic parts now treated from the standpoint of economic strategies? Patents are the front line of protection, innovation, and sharing. I want to take low-level genetic functions and recombine them to make new DNA programs. Think about a piece of computer code—How different would it be if you had to get a license for each piece of the code? Too many patents are being granted; we should be considering other sorts of legal technologies as well. A paper he

cited [A. Rai and J. Boyle, "Synthetic Biology: Caught Between Property Rights, the Public Domain, and the Commons," *PLoS Biology*, Nov. 6, 2006] argues against all these alternatives:

- Patents are expensive, slow, and exclusive.
- Copyrights are already horribly "munged" and potentially dangerous if misapplied (they last too long)
- Contracts—leaky and have high transaction costs
- Public domain—incentives; vulnerable to other approaches
- Sui generis—cost, could go terribly wrong.

["Munged" is a technical term meaning that some lawyers think copyrights never should have been applied in the first place, and the idea of applying them to biology is even more horrifying to them.]

Two points: 1. How can we, as a society, optimize ownership, sharing, and innovation, beyond consideration of patents and 2. A challenge to this group, what combination of legal and economic strategies would best support innovation in synthetic biology?

Risk and Security

How does synthesis of DNA change the risk landscape? You can get access to objects you couldn't before. Three classes of pathogens to which synthesis gives access include one that is locked up (smallpox), one for which the natural reservoir is not known (Ebola), and one that didn't exist until very recently (1918 influenza). Who are the folks with access to this technology? In principle, everybody. What are their intentions; do we need to do anything about them? Most are disposed to doing good. So the question really becomes, "What do we need to do to maximize that group?" Short-term challenges include avoiding remilitarization of biology. There is a low probability of this but high consequences if it were to happen. We don't want to shut down modern technology. In the long term, we must recognize that, inevitably, future biological technologies will be actively misapplied by small groups and individuals; how can we make this not matter? An analogy—I wouldn't be thinking about computer security starting from the assumption that no one would make a computer virus in the future. Let's admit that somebody will be making living viruses from parts.

Community Organization and Culture

Who are the synthetic biologists, and how are they looking for answers to some of these questions? Presently, they are not very well organized. Here is a picture of the third annual meeting of the American Society of Civil Engineers (from 1865) and today, 30 years after the invention of recombinant DNA technology, where is the American Society of Genetic Engineers? If you want to think about social norms, a culture of responsibility—maybe think about how professional societies could play a more active role than they have thus far; here's where engineering communities could bring in some interesting perspectives .

Societal Implications of Synthetic Biology

Where We Have Been Before, and Lessons Learned

Mildred Cho (Stanford)

I was a student at MIT right after the moratorium on recombinant DNA was implemented. Now we're back talking about recombinant DNA again. I will talk about a few situations that we can look at to learn from. There is now a variety of technologies that enable us to manipulate biological systems, especially the genome.

The Asilomar conference marks a profound event in the history of biological research. It was initiated by scientists and attended also by journalists, in Asilomar, California. It was sparked by a set of experiments that researchers contemplated (but hadn't carried out) that would entail taking DNA from the SV-40 (cancer-causing) virus and putting it into *E. coli*, a bacterium that lives in humans. There was a plausible concern about the potential for harm.

This led to discussions on whether to proceed with recombinant DNA research. Mainly, it was the scientific leadership who were raising these concerns. This resulted in a temporary voluntary moratorium on selected experiments. These scientists identified issues in terms of health risks. Many authors have written about such lessons since the late 1970s. Paul Berg (Stanford) commented that scientists took the initiative in raising the issue, and public trust increased because of the transparency of the dialogue. A criticism was the failure to consider the ELSI of plant and genetic engineering. So, one lesson here is that questions should not be framed only in terms of a narrow set of physical harms but the discussion should be broadened to include other topics that may not be best addressed as scientific questions.

Another topic brought up earlier was GMOs. Given the history of the Asilomar conference, how GMO research played out in other fields like agriculture showed a lack of organized discussion about agriculture and public risks. The trajectory of that research went in different directions in different countries. In Europe it led to the precautionary principle that places the burden on scientists to prove there are few risks; this is a different route from that taken for the introduction of other technologies. Another lesson from the GMO experience is the lack of trust in scientists and their willingness to acknowledge risk. When asked in a survey who could be trusted to talk about this, 26% of Europeans named environmental groups and 6% named scientists.

Our experiences with gene therapy and gene transfer present some lessons. The first gene transfer studies were done in late 1980s and early 1990s with a high level of review and oversight. They used an administrative model developed in the recombinant DNA era a decade before and then applied that model, which involved individual levels of review and high scrutiny. The field ran into trouble later, and some of those problems were summarized in a 1995 report commissioned by NIH to assess that agency's investment in gene therapy research. The committee was headed up by Stuart Moltkin and Arno Motulsky. One conclusion was that expectations were great and clinical efficacy was not obtained; thus, more basic research was needed. Overselling this technology led to the widespread perception of success that was not matched by what was achieved. This kind of outcome threatens confidence in the integrity of the field and may hinder progress. So, while the safety of gene therapy was better ensured with a high level of regulatory scrutiny, there still were problems with how these experiments were portrayed and our inability to meet these expectations. This experience has lessons for implementation of any new technology such as nanotech.

Another issue that came up in gene transfer was the role played by industry. This is not unique to biotech. Not long ago, a research subject at the University of Pennsylvania died on a protocol and the investigators, the university, and the dean of the medical school all had financial ties to the research sponsor. Science's ties to industry—a phenomenon now common in biology—attracted a lot of attention. A quote in a *New York Times* story about the death of the teenager Jesse Gelsinger noted that the family felt they were duped by scientists who cared more for profit than safety. Another lesson here: the importance of trust. This all happened against a backdrop where people were not well informed about gene therapy yet were in favor of it. There's a natural tendency to want to support future benefits. When asked if the benefits of genetic engineering outweigh the harms, survey respondents showed a drop from 65 to 55%.

Now we're in era of human embryonic stem cell research with a ban on funding and an acrimonious public debate. Scientists haven't been silent, particularly in California. They stepped forward to serve as advocates but haven't taken on ELSI. The National Academy of Sciences has recommended guidelines for oversight, but this was based on the research going forward.

Some emerging themes include the following:

- Scientists are well served by initiating and being involved in ELSI.
- Discussions shouldn't be limited to risks for humans but environmental risks also.
- Engage in broader concerns—ethical, legal, and societal issues.
- Portrayal of benefits should be realistic; it won't help generate trust otherwise.
- The biggest lesson: social context is always changing. If we were to have Asilomar today, it wouldn't be done the same way. Paul Berg says things have changed too much. So all our discussions are important, but to place too much emphasis on actual science, benefits, and risks misses the point. It's about the people: those

who do the science and the trust others have in those people. We've had similar discussions about synthetic biology and nanotechnology that are parallel in terms of risks and benefits. This points to the fact that the things we need to attend to are the social context and the players. Scientists should be a part of dialogue and think of issues in terms of educating the public. We need to understand why there are perceived lacks of benefits and perceptions of harm. We also need to understand that scientists are perceived as actors with self interests, that researchers may not be acting as fully ethical players, and that the role and perception of corporate interests and scientists are seen as being part of that. We need to build up trust in the scientific community to allow science to move forward.

Synthetic Genomes: Risks and Benefits for Science and Society

Bob Friedman (J. Craig Venter Institute)

We are doing a year-and-a-half study funded by the Alfred P. Sloan Foundation to explore how synthetic biology technologies might be used by, for example, bioterrorists. In synthetic biology, we construct large stretches of genes or whole genomes. I run the Venter Institute policy center. Our study partners are

- Venter Institute (Friedman and Michele Garfinkel)
- Center for Strategic and International Studies (Gerald Epstein)
- MIT Synthetic Biology Group (Drew Endy)

The study goals are to

- Construct and evaluate policy options to address possible adverse consequences of synthetic genomics.
- Evaluate the risks and benefits of this new technology.

The study is funded by the Office of Homeland Security, DOE, and the National Scientific Advisory Board on Biosecurity.

Potential societal concerns include the following:

- Bioterrorism
- Ethical and religious issues (Mildred Cho was involved in a 1999 study for The Institute for Genomic Research where some of these were looked at)
- Harm to the environment
- Lab safety
- Ownership
- Others

Scale: Oligos, Genes, Genomes

- Building blocks: nucleotides
- Basic unit: the base pair
- Oligonucleotide: 25 to 100 basepairs
- Gene: hundreds to thousands of base pairs.
- Genomes
  - Viruses: 1000s to 100,000s
  - Mycoplasma: 600,000
  - Average bacteria: 5 million
  - Human: 3 billion
  - Plants: typically billions or tens of billions

We are now at the point where we can synthesize any virus, although some of the larger ones are still very difficult. We can't synthesize a bacterium yet. The basic approach to synthesis starts with ordering shorter pieces of DNA (5 to 10 kbp). The Venter Institute wants to build a minimal genome on the order of the *Mycoplasma* genome (containing some 580 kb). We are attempting to take out the nonessential genomic elements and end up with a stripped-down bacterium. Then that will be put into an empty cell to see if it can reproduce itself. The reason is not to "create" life, as the press puts it, but to reconstruct life. It still means going from chemicals to being alive. We want to be able to do experiments in a high-throughput fashion to understand the basic mechanisms of life. There are many potential applications.

Early work at Venter Institute included synthesis of phiX174 bacteriophage that infects bacteria. It's a 5-kb piece of DNA, and there's a "cookbook" for doing this. It was funded by DOE.

We have had three preparatory workshops focusing on different aspects of synthetic genomics technology, looking at three issues: synthesis technology, risks and benefits, and governance. We also will hold a large invitational meeting that includes the policy community. Working papers (by staff and being commissioned) are being prepared and will be made freely available at the conclusion of the project. The societal concern focus has primarily been on bioterrorism and biosafety.

Workshop attendees include the following:

- A core group of 15 people for all workshops. Half were technology developers and users, and a third were policy types
- Government observers to observe and assist
- Additional participants to augment core expertise on specific topics

Participants are diverse and include scientists, engineers, social scientists, and policy analysts. But we couldn't have everyone at the table, and participants at the invitational meeting will help broaden the expertise and points of view represented. The study's focus is on risks, including the nefarious applications of bioterrorism and risks to workers and environments in the case of accidents. We are looking at possible countermeasures to bioterrorism and epidemics or pandemics. We felt it would be most beneficial to look at the new risks and benefits, but we keep coming back to "old" issues (i.e., the GM debate), and now we think the notion of distinguishing new problems from preexisting ones may have been wishful thinking. We aim to offer options for decision makers focusing on potential adverse consequences and to evaluate the pros and cons of each. And we aim to construct and evaluate options to address potential adverse consequences of synthetic genomics. These will include a "no action" option and options for governance (targets for possible policy interventions).

The first workshop was on synthesis technology. We examined both the raw materials and equipment needed to assemble DNA into long stretches and the knowledge or know-how necessary to do it. Two topics were considered:

- End-to-end look at interventions to reduce the threat of bioterrorism
- In-depth examination of software to screen orders to synthesize oligos and genes

To summarize, we examined production factors for genome synthesis to look for points of intervention or interception to deflect nefarious users (e.g., raw materials, sequence information, equipment, and know-how). We also examined a series of scenarios to see where one might intervene. Seven genes would be needed to reconstruct the 1918 flu virus, so we looked at whether there could be a way to flag a request for something like that.

The second workshop, which was just finished, was on risks and benefits. We examined incremental risks and benefits. We realized that we cannot resolve currently unsolved problems regarding conventional biotech, much less as-yet-to-be-defined problems imaginable in the future. These risks include bioterrorism and accidents. For benefits and applications, we need to understand the basic biology, both for countermeasures against bioterrorism and epidemics. There is a broad array of applications.

Some conclusions thus far:

- Bioterrorism

  - Today it's far easier to obtain pathogens by other means than synthetic approaches; in 5 to 10 years, this may change.
  - No policy intervention is fail safe.
- Biosafety
  - Are current oversight mechanisms sufficient and appropriate? OSHA and TSCA have oversight mechanisms for dealing with DNA: institutional biosafety committees. But new approaches present different challenges; a whole new group of folks are coming into the field—engineers—and they need to be included. We now have the ability to take pieces of pathogens and put them into nonpathogens. Our current biosafety systems deals with that somewhat, but the scale is greater than before.
- Benefits
  - Clear benefits for basic biological research
  - Some potential for countermeasures (e.g., DNA vaccines), but there's no silver bullet
  - Intense interest in applications (e.g., energy or drugs)

We don't want to overbill this. There is tremendous interest and excitement but it's not a done deal.

Third workshop at end of May will be on governance:

- Possible targets for policy intervention
- Technical controls—bioinformatics screening (e.g., black watch software). Other means? Registration of oligo synthesizers?
- Societal controls: institutional review, professional codes of conduct
- Research and information needs: how can the community and scientists help us understand levels of risk?

These three workshops will feed into an invitational meeting that will probably take place in late summer or early fall. The ultimate goal is to construct and evaluate options to address the potential for adverse consequences of synthetic genomes.

A Perspective on What May (and May Not) Be Coming Our Way

Something Wicked This Way Comes—Or Not

Pilar Ossorio (University of Wisconsin)

This is a complex set of issues and we should avoid simple-minded thinking (all "good" or "bad"). There's no crystal ball, and there's a tendency to make grandiose proclamations. A lot of predictions are simple minded and not helpful. We are hoping to avoid analyses that assume one impact or that will affect different sectors in the same way and over time. Societies, cultures, subcultures are complex dynamic systems with many factors that impact them.

There are ways in which synthetic biology and nanotech are extending trends we've had going on for awhile, and we may be able to make some reasonable predictions about what may and what may not happen by looking at related events.

There was one case in which Leon Kass (Univ. Chicago) and a radical feminist actually agreed on something, and they both turned out to be wrong. They assumed that new reproductive technologies would be bad for children and familial relationships. Both thought that "test-tube" babies would present a situation in which the parent-child bond was disrupted or denigrated, in the sense that parents would view these babies as a reflection of their preferences and thus might lose their ability to respond to them as separate individuals with their own needs. But the evidence shows that babies born with assisted reproductive technologies are not really any different, and, if anything, there are some hints that there are actually better relationships. This teaches us that assisted reproductive technologies didn't change the nature of children. This is not surprising—when a much-wanted baby comes

along, everyone is thrilled—it's a baby. The conception part is actually a very small component. It's useful to look at cases like this to extract some trends, some useful principles.

About synthetic biology—making a world—we've been doing this a long time. Now we're accelerating and extending the possibilities and maybe making new ones.

Some tools for prediction (described further below) include:

- Think about path dependence. The reception of a new technology will be path dependent.
- Use knowledge from social and cognitive psychology.
- Look for and model effects on social networks. With respect to the Human Genome Project, people weren't thinking about relationships and social networks as ways in which the reception to a technology is changed.
- Use a variety of analytical frameworks—need to try different approaches.

Social impacts are path dependent.

- Which technologies are introduced first?
  - Who benefits? If golden rice (containing more vitamin A to fight blindness) came out first, reception to GM foods might be better.
  - Which company or industry is promoting it and their reputation?
- Recent history of regulatory successes and failures
- Recent history of scientific successes or failures
- Impact of recent events on trust in government in general

Use knowledge from psychology.

- Heuristics
  - Information cascades, framing, available heuristic (an easily remembered outcome)
- Procedural fairness. There's a whole world of social and experimental psychology looking at what factors of an institution cause people to judge it as fair or not
  - Affects views on legitimacy of agency (authority) actions
  - Affects willingness to comply with rules

There are reproducible data available that show if people feel they have a voice in the determination of a policy or a range of policy options, the more they are likely to feel that something is fair. Ask whether existing mechanisms give people a voice.

Social Networks

- Interactions among people who previously did not interact may create opportunities for new institutions (self-organizing or intentionally organized). A higher frequency of interactions can fundamentally change relationships. For example, wireless technologies are changing our stereotypes of male relationships, that they do things together but don't talk. Now they talk and e-mail all the time.
- Changed context of interaction can change nature of relationship.

Possible Frameworks for Analysis

New technologies for people--- or "new" people

- Doing the old functions better (medicines)---or doing something new.

However you frame it, there will be short-term impacts vs medium-term vs technology influences.

Some Possible Productive Future Activities

- Use value theory (see below). As a society we are resistant to this kind of conversation. We're pluralistic and instead have a public discourse in which values are hidden. People have been working on this for a century and it's relevant but it's been ignored in bioethics.
- Develop and test institutions and mechanisms for pubic discourse.
- Develop new governance models (see below) and study old ones better. The law and policy world talks about governance and not about regulations. It's used more generally and means all the ways that shape a certain behavior. In this case, scientists and producers of technology. There's a body of literature. There are models there to examine how agencies should relate to people.

Value Theory

- John Stuart Mill asked: is it better to be a miserable person or a happy pig? To what do we attribute importance and significance? Articulate areas of agreement and disagreement.
- Articulate why we think some future worlds are better than others.
- Consider possible transition costs among this world and desirable future worlds.

New Governance Models

- Cooperative. In a lot of agencies that attempt to develop structures that don't rely on regulations, various parties do cooperate.
- Standard-like strictures rather than rule-like strictures.
- Not a strong enforcement focus. If you don't have rules and rule-like form, it's difficult to enforce.
- QI-type approach to regulation.
- De-biasing through law and governance. There's a literature forming about how we can use the rules to counteract cognitive short cuts and create a situation in which tradeoffs get better consideration. What are the implications of having DOE and government shape how people think about something?

The Intellectual Property (IP) landscape

Lori Knowles (University of Alberta)

I'll try to show the space where synthetic genomics might run up against IP.

Background of my talk

- Societal issues with respect to IP generally
- Societal issues with respect to IP and genomics
- Points of convergence or distinguishing factors between recombinant and synthetic genomics
- Is there anything new here? The short answer: there isn't that much new. Most of what would be societal issues are going to be very similar to what's happening with gene patents.

Society and IP Issues

- Concentration of ownership with respect to perceived public good in private hands
- Blocks to access thru higher prices or limited licensing
- Blocks to innovation
- Nonresponsiveness to values (public health)

I will present societal views of gene patents and then ask if there are corresponding or new issues with regard to synthetic biology technologies.

Gene Patents and Society

Society takes different views on this.

- Privatizing is a common good. Human DNA is our common heritage and biodiversity is a common good.
- Exploiting vulnerable individuals or societies. Bioprospecting vs biopiracy. Relationship of tissue to source.
- Hindering downstream innovation
  - Through patents on SNPs, broad gene patents issued
  - Creating thickets; Opportunities missed and other research not done
  - Blocking further innovation and improvements
  - Harms to human health
  - Higher drug prices (AIDS)
  - Blocking access to necessary testing (Myriad)
- Harming the environment
  - Gene flow (Schmeiser vs Monsanto case); gene "escape"
  - "Terminator" technology (sterility). The public debate doesn't correspond at all to the scientific debate. Scientists feel it's irresponsible to release something without "terminator" technology. Public says that's unnatural—you look at a plant and it looks natural but it's sterile—this bothers people.
- Creating new organisms (transgenesis)
  - Crossing species barriers
  - Playing God—fluorescent mice
- Owning life
  - From living organisms to higher life forms to human cells. Harvard oncomouse was not held to be a "manufacture"—the mouse was not subject to IP. but the process can be. They said you should not be able to own higher life forms. Jeremy Rifkin filed applications to the PTO to push the system to look at human-animal hybrids. In France there is no ownership of human DNA and body parts.
- Immoral uses
  - Nonbeneficial utility. Chimeric organisms—the benefit is not making it through to society.

Society and Synthetic Genomics

Is there something novel here? What threads can we pull out of genomics?

- Privatizing as a common good? Synthetic DNA will have less resonance than recombinant DNA with people. I don't think we'll see friction with society here.
- Exploitation of vulnerable individuals or societies? Not really.
- Hindering downstream innovation?
  - Yes. Ownership of basic biological functions creates a directly analogous situation where there is balkanization of these functions that impedes research. Could necessitate negotiating a thicket of thousands of patents.
  - This situation is worse now due to the pace of the technology.
- Harms to human health
  - This is a significant issue. Blocking further innovation and improvements. If we get a case where it happens to block the common good, it might change something.
- Creating and owning new organisms

  - Conflation of the higher organism question with synthesis and synthetics. If you could synthesize a person, people will talk about it. You can't say this is human so not a synthetic manufacture. This is different. Can be a cloning type debate.
  - Creation of chimeras—brand new. We've always been uncomfortable about that and how it fits into IP is difficult. Escape of novel organisms.
  - Evolution.
  - Engineered sterility or death
- Immoral uses
  - Creating novel viruses and organisms that could be used for bioterrorist activities

Beyond Patents

- We'll be dealing more with an information platform than the current materials platform. Drew Endy said ultimately the information will be more important, like what is happening in the music industry.
- Copyright or patenting
  - Stretching copyright to fit
  - Research exemption for copyright but not for patenting
  - Copyright length could be even worse? Straining to see where these things should fit.
- Sui generis
  - Limited time frame or licensing restrictions. Precedent: semiconductor chip.
- Open science model—Drew Endy does this with his Biobricks (modules). Put things out there and get people to use them, keep them as a public good.
- Importance of cultural architecture along with legal tools so if you want to create an open source you need to get in at ground floor and create the culture with those people. That has possibilities with these groups—it's a small community and they tend to talk with each other.

A Few Predictions

- The first application that grabs social interest and attention will likely surprise us.
- Any talk about synthesis of humans and higher animals outside the lab will likely be misinterpreted, and this will merge into cloning debates.

View from the Bench

Susan Ehrlich (Arizona Court of Appeals)

Forgive me if these remarks are not as developed as I would like. First, I am only a last-minute substitute. Second, much of what I would have liked to say has been said already.

I foresee innumerable issues that will be legally and intellectually fascinating. A court, however, does not so much shape law as it interprets law in the context of the case before it. This means that the court is always behind the social curve. A public perception of necessity or adverse events usually precedes regulation. In other words, laws are the result of our democratic (and republican) process. Their societal implications are matters of social perceptions of responsibility and propriety, matters different from their legal implications. Indeed, the law neither does nor should encompass every ethical responsibility, every moral duty. Rather, the law is a social contract. And I am of the opinion that our social contract—the Constitution and the Bill of Rights—is the most glorious that a people has yet developed, because it is a viable social contract.

The events of 9/11 made us sensible of our vulnerability. In an obviously different context, the pace of discoveries in the life sciences also has made us feel vulnerable, concerned about the unknown. In this environment, it's

very easy to succumb to the false promise and sense of security that we need more regulation, although within the last century we saw that strict regulation can be utterly ineffective (i.e., we amended the Constitution to ban liquor and then we repealed the amendment). Indeed, overly strict regulation is likely to be double-edged. My understanding is that, in the U.S. Code, there is a prohibition addressing the variola virus, one which makes it more difficult to develop countermeasures, including vaccines. I view law as a management tool and judicial decisions as a mechanism for filling the gaps because laws cannot address every factual situation. Even all the excitement surrounding nanotech and synthetic genomics won't necessarily change the type of legal issues.

Examples: Bioterrorism is a new crime, as is the use of certain biological agents. While the bioscience component may be a new element, this will not change the underlying nature that there has been a crime, the murder or assault of one person or many persons, or a tort. In healthcare, the standard for appropriate treatment is the same whether it is the provision of a tetanus shot or gene therapy. And the patent process, which is outdated, will present challenges.

I have signed opinions with which I disagree because the principle with which I agree most is deference to the legislature. Society has acted through its representatives, who have passed laws and regulations. Now that I have told you how limited my sphere is, I'll change from my black judicial robes and put on black preacher robes. It's important for judges to be educated, as well as jurors, parties, and those who will read about the case and its disposition. Rules of evidence are applicable to scientific and nonscientific evidence and judicial interpretations of those rules, all of which operate as a practical matter to make the judge a gatekeeper for the jury. But we're dependent on the lawyers before us to educate both us and the jurors. This brings us back full circle to scientists—who have a duty to be educators from their (lab) benches, an obligation that well exceeds the needs of individual cases. The expertise that scientists possess obliges them to think seriously about these issues and participate in the public discourse. Without such engagement, we will not have societal understanding or, concomitantly, good laws and regulations.

PANEL DISCUSSION: What are the Key Issues?

Endy, Cho, Freidman, Ossorio, Knowles, Ehrlich

Dan Drell: The first publicly recognized recombinant DNA application was human insulin, which had no down side. What in a comparable sense might be the first publicly acknowledged success of synthetic biology?

Drew Endy: Antimalarial treatments outside the United States. DNA vaccines in people in the United States.

Question for Bob Friedman (Venter Institute): Should we think of societal implications that have less risk but may be of greater frequency? For example, if we can correct genetic defects, what of diversity and how do we know if the original differences (i.e. mutations) had a purpose? How do we discuss and assess more the fabric of society, and how can we incorporate that into this discourse?

Friedman: So the question is why take on first-order issues like bioterrorism and harm to the environment. Synthetic genomics and biology hold great promise for understanding how cells work, and if this knowledge emerges, it will extend to many other applications. We need to get past the first step to allow society to move in that direction. Don't know what intermediate issues will be. I came from the legislative side of Government (i.e., the Congress), where we worked on reactive issues. I'm a believer in adaptive governance—quality-improvement government. That's all we can do.

Pilar Ossorio: There's another issue here. If we want to spend time and money, people need to discuss the things they care about. We need to figure out why we want to have these discussions.

Susan Ehrlich: I saw an ad on TV for a show about Avian Flu, a drama showing people with masks in the street and general hysteria. It was compelling. It's easy to discuss bioterrorism, easier than other discussion topics. With all the information that comes at us, it's an easy substitute for thoughtful discussion.

Ossorio: There's a reason why it's important to have a session that focuses on value and what kind of society we want to have.

Mildred Cho: It's a good point about lower drama, more pervasive issues. If you have a discussion of values, the scientific community doesn't have a lock on that, and other voices need to be brought in. They did studies on people's views on having a predisposition to sickle cell disease. Unless you include people who have this disposition, you couldn't anticipate the opinions. For example, if you talk to people in United States who are carriers, they don't necessarily think of it as bad but rather see this DNA as a way of validating their lineage to Africa. They are members of a valid group whereas, in the United States, they feel disenfranchised.

Question: A more cooperative, less enforcement-oriented regulation is an interesting model to consider when some vocal advocacy groups are calling for more regulation. Why do you think it would work, and how would it affect trust in government?

Ossorio: I don't know that it would work; it's a model to examine. They are negotiated regimes, so activists might find the structure acceptable if they are at the table.

Ehrlich: There's the Prohibition example. The point is, I am worried about the U.S. Code being used for micromanaging. There are fewer issues having to do with Federal regulations because they are more easily changed and thus can be more exhaustive. Fear is curtailing the openness that's essential for research and our ability to counter mischief, and much of this has to do with an easy response to a public that is not well educated.

Drew Endy: Regarding the code against smallpox material, people didn't know about it for 6 months. I was surprised by the story in *Science*. This screening technology that puts a filter in front of synthesizers is worrisome. It needs to be embedded in groups of individuals.

Ehrlich: Also, it gives a false sense of security.

Friedman: We're dancing around different issues—how and where technologies are used, regulating the research environment, and regulating the production environment to produce products. You look at governance tools used in a particular environment. Different sets of regulations have been experimented with since the 1970s, and there is no perfect instrument. There are better instruments for specific purposes. The goal is to try to carefully match the instrument with the problem. When a new and r rapidly moving technology comes along, we agree on the need to be looking at more flexible instruments because brittle approaches are woefully inappropriate.

Doug Lowndes: The courts have a lot of flexibility in dealing with infringement—can courts help in terms of infringement penalties?

Ehrlich: The Blackberry case shows us the courts can't. Blackberry settled but there seems now to be discussion about whether the patent was viable. That creates a lot of commercial unease—no finality. Also there not being one patent claim but hundreds in case one is viable. But it is not the courts that can change the law.

Ossorio: The court has developed a doctrine of nonobviousness as a condition for a patent, and this is intended to be the hardest hurdle. If you can develop that doctrine to find more patents not valid, it would create improvements. With patent thickets, part of the problem is incremental knowledge improvements. It won't stop PTO in terms of their approach in looking at patents.

Endy: He says if there's a better option, we should explore it. He'll propose two research projects: (1) undercapitalized companies should document projects they didn't pursue, and (2) a strategy should be worked out for incentivizing innovation around low-level functions of biology, recognizing the uncertainty of that. Need some analytical work to present a framework to make good decisions.

Ehrlich: We also have to decide on interests in globalization—who can patent, file, who can object.

Robert Cook-Deegan: The problem is figuring out which things to focus on that matter in the real world. Do we have a short list that could help think about this?

Endy: I listed four in my talk from the perspective of a practitioner.

Friedman: We need to clear out the noise—get rid of some bioterrorism issues (that's under way), lab safety issues, looking at risks to the environment. Past that, the next candidate is to figure out what people are going to do with this technology. We don't have a good sense of that yet.

Lori Knowles: We are looking at one area where we have a body of law and problems that sifted out. I'd like to take it further like biosafety convention on modified organisms—and extend to synthesized organisms. Are they the same, are they different? Look at the tools we already have, IP in just one area.

Cho: We need to talk about purpose. What is your purpose here? Preservation of scientists able to do science? I wonder about this when we talk about public dialogue. What does it mean to be bias free? Maybe bias is good (emotion impacts moral decisions, and that's not necessarily a bad thing). What's the goal of looking at societal impacts? How much do we want or need to understand about what counts as an impact?

Ossorio: When you say take on issues that matter in the real world, they matter in terms of what people care about.

Charles Rubin: If you have a critter that glows green and you patent that, if the price is too high to use it, you ask if that's the only way to glow green. You encourage ingenuity in a different way.

Endy: There's the cost to invent, cost to refine, cost to work around (is this the only instance of this function?). You encounter a full spectrum from free to infinite costs. For example, with a low-level biological function like engineered DNA binding proteins—all IP will be locked up in a single company. Business model is to deliver a product through big pharma for single-use application. A patent on an early technology will play out over a long time scale.

Ossorio: The patent law does encourage "inventing around." We need to figure out what it is we have to fix.

Knowles: This technology is starting in an environment different from other industries. Basic functions in those other industries are not tied up.

Rubin: So it's something like locking out the "Print" command to everyone else.

Endy: Need to consider deploying a complete strategy around the costs.

Ossorio: That's where NIH ELSI is moving—looking at what are good licensing schemes.

Tuesday, May 2

Perspectives on Societal Implications for DOE's Office of Science

Ray Orbach (Director, Office of Science)

My perspectives are not off-the-cuff remarks because the Office of Science has been involved (through Dan Drell's ELSI program) from the beginning in this, and over the years we've developed sensitivity to these issues. About a year and a half ago we talked about a path along which to proceed with this in such a way that the science was enhanced. Because I'm a physical scientist, sometimes ethics comes in at the back end and is viewed as an inhibitor. Is it possible to integrate ethics in the beginning?

There are some similarities to how Office of Science functions with regard to safety. In DOE we have integrated safety management (ISM) from the outset: as an experiment begins, safety is built into every aspect of the process. Ultimately it's cheaper, more effective, and fairer to workers than waiting for an accident to happen and then trying to fix things. ISM is a process that involves people in the safety business at the same time researchers are figuring out their paths forward to new knowledge. National security has picked this up and, for a number of years now, they have been instituting Integrated Safety and Security Management. A safe and secure work environment helps those carrying out the Department of Energy's vital tasks, and there's a real feeling of camaraderie among those involved as well.

I believe ethics should be treated similarly. We all read the scare books on nanotechnology and global warming; there supposedly are lots of scary things out there that could turn us into monsters instead of scientists. It gets our backs up, and, before you know it, there's antagonism and opposition. We want to chart a path forward that enables us to integrate ethics into every aspect of the operational fabric. We want to recognize that ethics management will enhance the science and that the relationship should be supportive, not punitive. We're struggling with nanotech, which has gotten a lot of press and fears, and genomics (which has gotten a lot of hype). These areas are major foci for Office of Science , which is approaching nanoscale research with five major facilities at national labs; these will come online in the FY 2007 budget. At Lawrence Berkeley and Oak Ridge national laboratories, we're well on our way to opening nanoscience centers; at Sandia and Los Alamos national laboratories, nanoscience centers will open in the summer. The operating budgets are around $19.2 million a year, so it's not modest. This will enable people to come from all over the world to carry out their research, starting at the atomic scale and moving to the macroscopic scale. Computational facilities in existence now can function over the full scale of material sizes. A new industry is coming together, and the opportunities are enormous for both a new science and for benefits to the nation. The risks are enormous as well, and it's important to integrate the ethical perspective into the scientific fabric.

Here you're going beyond that to deal with the future also. We need you to outline the issues that we will face to define this territory for future integration. This is not regarded in a defensive posture by Office of Science. We believe in this as an essential feature of our function. It will make nanotech and the other realms of advanced science that we support a more exciting and productive area.

My first experience in this field came from a remarkable paper in *Science* coauthored by Mildred Cho, from the effort started by Craig Venter on synthetic biology. This was the integration of an interesting group of tough individuals who were considering issues around artificial life. More recently, Craig Venter and Hamilton Smith were able to synthesize a phage in 2 weeks. They are doing very exciting things at their Institute, and the opportunities for all of us from their work are superb. But in that initial step arose the question, What happens when a microbe gets out? The trick here was to design a genome that would die if it left the lab, to make it a built-in feature from the beginning, and this actually reduced the difficulty of the synthesis, so here's an example of ethics enhancing the science.

There's a larger issue here—How do you, in our social fabric, create an environment and a trust in the public that enables the science to proceed more effectively for the public interest? It's pretty easy to use scare tactics, and it's much harder to convince the public that anticipated fears have been dealt with. Lack of trust in government is what we wrestle with all the time. There's a constant need for a policy of openness with respect to publication and dissemination because, as soon as people think you're hiding something, they don't believe you and that distrust persists for a long time. A good example is the tritium leak at the Fermi National Lab. Tritium is a radioactive isotope of hydrogen that the body can absorb like water. Fortunately it has a relatively short half-life, but you shouldn't mess with it. Scientists at Fermi Lab detected tritium in one of the creeks around Fermi that was at an extremely low level, but the sensitive devices there could pick it up. It was orders of magnitude below what was allowable. Fermi lab immediately informed the public about the leak. The lab did get cited by state of Illinois for a violation, but, because of their honesty and openness, there's a sense of trust in the community around the lab. Handled differently, the lab could have been shut down.

So the issue of trust is critical. There was an element of trust that enabled Craig Venter to go forward in a way that was helpful to him and to us. There wasn't a Congressional investigation about what we were doing with our funding. You have the strong likelihood of opposition when people become afraid. Regarding the program Genomics:GTL, Ari Patrinos and I once spent an uncomfortable Sunday before Congressional committees about who had jurisdiction on the word "life." There was some wording that was implemented for us, that the DOE Office of Science should have nothing to do with research on human health. Thus there are political consequences that emerge from the lack of trust of what agencies may fund and what the consequences will be.

I hope this will be the beginning of the kind of relationship we will need in the long term. We don't know what we'll find in nanoscience or synthetic genomics. We know there's enormous promise in both fields. We have an inkling of the opportunities but, to be blunt, we're still learning what happens at the atomic level. It's a very

different universe with very different behaviors. Gold at the nanoscale is an active catalyst yet very stable at the macro scale. The ability of microbes to perform remarkable functions may hold surprises. We need to build ethical thinking into the fabric of these investigations so we are capable of structuring our work to benefit society. Another reason is so we can explain to the public what we're doing and how we've gone about it. Trust can't be achieved by advertising; it has to be earned as part of the research-and-development structure. It is hard to amass but very easy to lose. Thus, your work is very important.

This meeting I hope will lead to a relationship as we proceed toward these opportunities. It's broader than nano and genomics, but this is what we face now. There are issues out there that will be troubling to people. We have a broad base of support for science in this country. We'll be involved in issues of creation. Wait until we start talking about this when we get pretty close to what happened at the origin of the universe. You can foresee an environment where people may be afraid to find out.

Questions and Discussion

Susan Ehrlich: Given your commitment to ethics and responsibility, how do you plan to implement this from your new position [Under Secretary for Science]?

A: It's the first time a person will hold this position—DOE Under Secretary for Science—and it's scary. The Department does everything it can to make sure communication is inhibited across programs. We use the word "stove piping." I've been working to talk to other programs. When the new Assistant Secretary for Fossil Energy came, the first question he asked was, How much will it cost him? There's a fear that this will impact budgets across the Department. The Under Secretary position will give me the authority to integrate science into all programs including NNSA as well as nondefense programs in the Department. That's what I was alluding to when I mentioned before that there are broader issues than even genomics and nanoscience. There are issues associated with nuclear weapons that are as fundamental in terms of ethics as one can address, so the Under Secretary will have responsibilities across the Department. The idea is to integrate science into the whole Department of Energy fabric and that means, along with it, ethics. In some ways the Office of Science is "cleaner"—we're all research—but the rest of the Department is involved in development and deployment, and then those issues are front and center. Think of the "reliable replacement warhead." What is it—a new weapon or an old one that's more reliable? The ethics issues there—treaties and the positions of the United States—are serious. They have not had the kind of meeting that we're having here. That's one example of what I'd like to do across the Department, but there are many others. So what you're doing here will have to extend beyond just Office of Science throughout the rest of the Department. The Secretary of Energy feels strongly about this. When I talked about setting a pattern for the future, I had in mind a body of people similar to you here, who know how to work with one another; we may be calling on you to help us in the future. There are some very interesting issues, especially in national security, that the public needs to examine in the same way we're talking about here and I think will make the programs better as well.

Tom Vogt: DOE has an elaborate mechanism when it embarks on new facilities and ventures. The various critical decisions have to be mapped with roadmaps and otherwise. If ELSI would be implemented in such a process as you speak of, it would require an ELSI roadmap at an early stage, integrated into Critical Decision (CD) 0-type decisions and continually refined during such a process and this is not being done currently. So when you say you want to integrate these issues, would it be along those lines?

A: Our ES&H [Environment, Safety, and Health] program is suggesting that we integrate safety in the CD process. It's exactly why this meeting is being held. They've taken safety integration across the CD tree, 0-4. It would be very interesting and appropriate to integrate these kinds of ethics deliberations. Construction is just a vehicle for production of something—we are constructing nanocenters. But if at the end societal fears mean they can't work, you can't turn them on, what good is this? What you're doing here is to help us figure out how (it's true we're pretty far down CD structure to integrate ethics now—we should have started at CD0 but didn't). In genomics we can do this. In Genomics:GTL, this summer, we'll be issuing a solicitation for two bioenergy centers on the recommendation of the NAS. This will be our attempt to get to CD1. So what you're doing now in genomics can be built in. For the CD process, it's a little late but never too late. Now that

I'm talking about this, I realize that we will actually not use the CD series for that because we want to avoid construction. We'll be setting up centers, there will be an Funding Opportunity Announcement this summer, and we are requesting letters of intent by the end of the calendar year (with proposals due early next year) and making awards a year from now. We need to build in these considerations at the time of the award or maybe even at the time of the announcements if we can work that quickly. We will do that in areas that aren't necessarily CDs 0-4 but are comparable. We're talking about leased space for these Bioenergy Research Centers. There will be other CDs that we will be going through, and I'd like to see ethical perspectives integrated into them. It is interesting that safety has already proposed this for our process. We need help on this to do it in a noninhibitory way, in a helpful way that enhances the construction process and the resulting science.

Why Do We Need Ethics? What Does It Actually Contribute?

Bob Cook-Deegan (Duke U.)

We talk about the early history of recombinant DNA in our classes to glean lessons about social responsibility in science. It's not an entirely simple story. It's not clear the "crisis" at the time was as severe as it appeared to be, since microbiologists had been working with extremely nasty microbes for some time, but it was new to molecular biologists. If the involved scientists had talked to their colleagues in microbiology a bit more, they might not have been as worried because there were practical things they could have done. But potentially nasty bugs (common to the experience of other researchers at the time) were new to the molecular biologists, and grounds for concern were very real.

It was significant that insulin and growth hormones were the first human genes cloned. These were the genes associated with violations of the self-imposed moratorium. So, documented violations of guidelines gave birth to the biotech industry. This story was told by Steve Hall and involved Eli Lilly and the University of California. It's not an entirely happy story, and it's relevant to today. One reason it's not known is that the violation was kept secret by U.C. and NIH. This happened partly because there were 16 bills pending in the U.S. Congress that would have imposed legislative oversight of recombinant DNA research and the scientific community, and the NIH didn't want them to pass. In fact, NIH's creation of RAC was probably the best outcome, but it's an ironic and deeply conflicted story.

Another story is about the birth of the DOE ELSI program. Under the directorship of one of Ray's predecessors (William Happer), a genome program manager, Ben Barnhart, attended a hearing where Senator Al Gore was asking James Watson (of NIH) and Robert Wood (Acting Associate Director for the Office of Health and Environmental Research, the predecessor of today's Office of Biological and Environmental Research) about their commitments to ELSI. At that point the momentum behind NIH ELSI was strong and they were pledging 3% of their genome budget to ELSI; DOE hadn't decided what to do. It was obvious where these questions were going—it was clear that all were in agreement on ELSI being a good idea. The only one not convinced was Bob Wood of DOE and he took some browbeating for it. Why is this significant? It took Congressional pressure on DOE to create an ELSI program. That hearing was not the end of the story. At the joint NIH-DOE quarterly meeting of advisors after that hearing, Ben Barnhart again expressed trepidation about DOE supporting an ELSI program. Jim Watson told him Congress would "cut him off at the knees" if he didn't, and the directors of genomics at Los Alamos, Lawrence Livermore, and Lawrence Berkeley national laboratories all agreed. So the DOE ELSI program was grudgingly inaugurated.

So what do you get from an ELSI program?

You get a combination of representation, perspectives, and research.

- It's a process of thinking about science that opens it up to voices at the table that are not scientists. It brings in social sciences and humanities and it matters because people who do think about those disciplines think about the implications of the science in a different way from scientists. And those who bring "real world" perspectives on problems, for example, groups concerned with specific diseases, bring urgency but also concern for end-users of the science. They sometimes criticize the science. The question is, Is that criticism fair?

Whether it is or not, it does bring a new set of perspectives even as you are planning the science. And like it or not, science is a political enterprise, dependent on public funding and hence public support.

- It generates resources for doing research. And it creates folks who think about those issues for a living, who get paid to worry.

Why does it matter?

- It helps discipline how you do and think about the science and it may influence what you do.
- It also helps folks think through the applications of the science.

I'll give some examples of where it could have made a difference and didn't and two cases in which ELSI research has made a difference, one where policies may change and another where it's still in play.

First example: The Human Genome Diversity Project (HGDP) and the social debate about race. Pick up Jenny Reardon's book—*Race to the Finish*. She's an anthropologist who followed this study as it was happening over the better part of a decade and has written a book about the process. The questions behind the HGDP were interesting—how are current populations related to those of the past, and where do we come from? We know it was from Africa at some point, but what about in the intervening millennia? How and when do you choose to draw the line when naming your ancestors? Proximal to this science looms a distressing history of misuse of human categorizations. The Holocaust is the searing event of 20th Century, and it's coupled to racial hygiene and that is coupled to eugenics which was deeply embedded in human genetics. That history matters to genetics and science and the humanities. HGDP was taking an interesting question and proposing to probe it technically, but it came a cropper at the hands of the political issues surrounding it. The population geneticists and anthropologists would have loved to duck the issue of race. But they could not, and their boat got sunk in a political storm they had hoped to avoid but took few measures to steer around.

The problem the project encountered was not that the science was bad, but it had failed to take into account a much broader social debate and a much richer literature about the social meaning of race. Racial concepts do overlap with biological notions of race but are not reducible to them.

You can't understand the significance of decisions you're making on a technological level unless you understand the history of the words you are using. And you need to think about the history of the concepts that your science is feeding into and how the people you are explaining your results to will understand them. Jenny Reardon tells a sophisticated story about how we think about race in our culture, and in the United States, it's different from Europe or Brazil.

Culture, with all that means, makes a big difference in how the science is interpreted. And in the end, HGDP encountered obstacle after obstacle, largely because of the politics surrounding this extremely volatile notion of race. Lesson: it would have been smart if we thought about bringing more voices to the table when we were thinking about the science. It would have been smart to know more history. It would have been smart to know how American Indian tribes must guard their autonomy zealously in light of history and how science could threaten the processes by which they even determine their own membership. Listen to the voices that are not from the lab next door. There's an analogy between what we're talking about and synthetic biology and nanotech. I'll make that connection at the end of my remarks.

A second example of ELSI making a difference: Mildred Cho and Jon Merz's work is doing very simple things, keeping track of patents and diagnostic genetic tests and surveying what people say they are doing. Can you put together a complete story about what's going on in IP based on this? No. But there's enough information to identify a problem in diagnostics. We don't need a lot more evidence that there's a problem. Some cases show how the way patents are being used is getting in the way. Some labs have abandoned testing. It's more expensive than it needs to be, there is a hassle factor in having to ship samples to patent owners because that's how they've decided to configure their business regardless of health system efficiency, and there's little evidence that we have more innovation or higher quality as a consequence. Indeed, quite the contrary. That points the way to solving a problem—either stop patenting the way we do or get patents and handle them differently through licensing practices. Empirical information is playing into this, arguing for how we should license our

diagnostic patents in the future. Duke is one of the problem places, and we've discussed whether the ApoE genetic testing patents should have been licensed as they were. So these data matter.

A third example is under way right now. We've had many discussions over the years about the potential for genetic discrimination. This was one of the original "sanctioned anxieties" (to use Diane Paul's apt term) of the ELSI program as it got started in 1989 and 1990. One argument is that genetic discrimination is not really happening and in fact we don't know how significant the problem is. We have pretty good data on how the *perception* of the risk of genetic discrimination alters behavior for taking one gene test or another. We also have some empirical information about the market for long term care insurance. There's no evidence for genetic discrimination, but there is some preliminary evidence for the potential for adverse selection based on people knowing their risk of developing Alzheimer's disease in the wake of getting high-risk test results from ApoE genotyping. If they have the type 4 allele, a preliminary study suggests they are more likely to change their insurance-seeking behavior—specific to long term care insurance (there are weaker, but not statistically significant, effects for health insurance). This is a genetic test for risk of a disease that accounts for a significant fraction of long-term care use impinging on a private voluntary insurance market. This perfect storm sets up the potential for adverse selection. What's going to happen? If you're an actuary for a long-term care insurance company, you're going to be paying attention. You're either going to set a price by assuming everybody is high risk, or you're going to stratify to take advantage of the fact that you can get information about that person's risk before you offer them insurance, and you'll offer high rates for high-risk people and low rates for low-risk people.

Is this a good or bad outcome? It's the outcome we'll get unless we have a social consensus that we should subsidize long-term care insurance for everybody. It's what we will get from current policy. This conflicts with the notion that you don't choose your genes. Is it a problem? A voluntary private market could drive us to pay for our risk as opposed to the intuitive sense that we shouldn't do have to do that if it is beyond our control. This pits actuarial notions of fairness (pay according to risk) against "behind the veil" notions of fairness (you don't choose your genes, so should not have to pay for risks associated with them). This will play out in real world, assuming that this study is borne out. The study needs to be replicated but it's a foreseeable problem This is evidence that there is a real problem of adverse selection if ApoE genotyping becomes common. If so, it will probably play out in the real world as actuaries will use the data and change policies; then the world will need to react to that.

This is how policy usually works. A problem arises, and the political system reacts. You can say it's the ELSI program that caused the problem because its research led to finding the problem of adverse selection, but it's a good thing to know that bad things are happening in the world. I trust in the deliberative process of democracy if you give it enough time—three decades and we'll be fine. OK, so give me five decades (and I'll be dead and you can yell at my kids if it's still a problem).

Those are three examples for why an ELSI program matters in the real world. So, turning to priorities from yesterday's discussion, I'd like to comment about synthetic biology and nanotech. There will be two big areas of concern different from other things we've talked about. These are in two general categories. I looked at Drew Endy's suggestions for priorities, and it fits under these general umbrellas: the notion of dual use and a set of questions about innovation and intellectual property and ownership and how the capitalist system works with new technologies.

"Dual use" is being used in at least three different ways, each rich with policy implications. The first meaning has gotten all the attention—dual use meaning that well-intentioned science is used for nefarious purposes. The science is intended to understand how nasty bugs work and how they can harm or shorten people's lives. Science is expected eventually to guide ways to prevent bad things from happening in the natural world by understanding how these bugs work and affect human hosts. "Dual use" is when I publish some information that is intended to further knowledge for everyone's benefit, but other people in a cave in Afghanistan can use it to create a nasty bug and harm us. It is using good information for bad purposes. That's the dual use that everyone's been thinking about, and it's real. It's something that four NAS reports focused on in the last 3 to 4 years. It's an issue that's going to be really hard to contend with, that will hit big time because these fields are rife with incredibly promising applications. Partly because of that, they have all sorts of foreseeable nasty uses. We'll have

to think about this issue, and any solutions we devise will look like processes and procedures that we trust. So we'll develop criteria for thinking about them and processes for dealing with those issues that are not unlike the judicial system; they are likely to produce a form of scientific regulation, probably self-regulation a la recombinant DNA oversight to begin with, at least. So we can expect some kind of review for dual use in the process of funding and publishing scientific results about virulent pathogens and technologies for dispersing them.

Another dual use is getting a lot of attention at my institution (Duke). Many technologies that can be used for dealing with anthrax or developing vaccines rapidly for an outbreak of something that's affecting (or threatening to affect) people in the rich parts of the world could, with a bit of effort, be just as applicable for all sorts of diseases that kill a billion people on the planet, mostly those living in poor parts of it. Those people can't afford the new technologies. The benefits for people in the developing world won't happen without policy interventions, and people need to be paid to intervene. Examples: When you turn your attention to making technologies cheaper, it can sometimes work. Drew Endy referred to Jay Keasling's work. Keasling's trying to make an antimalarial drug much more cheaply and make it more widely available. That sort of use needs to get funded. You can think of all kinds of bugs causing bad outcomes all over the world. It's getting attention from entities like the Bill and Melinda Gates Foundation and dozens of nongovernmental organizations. That domain of policy is relevant to lines of research on pathogens and host reactions to them as well as technologies for developing vaccines and drugs at low cost. Whether DOE wants to take responsibility or even think about it is up to DOE, but it's a good idea. It matters.

A third type of dual use is destructive use by our own governments, a misuse that happens systematically behind closed doors that could be avoided if done in the light of day. This is an uncomfortable thing for DOE to think about, but it's a big deal. The anthrax that was used in the attacks in Washington, D.C., was cycled through our own defense establishment at some point. It came from Fort Detrick, and it does suggest that sometimes by increasing the amount of government activity in an area you can worsen a situation in the real world. We could be boosting biodefense capabilities but simultaneously increasing probabilities of a misuse. It's ironic but it could happen if we don't pay attention to that set of issues. It could happen even if we do pay attention to them. If I were to pick one thing, this is a high-probability event—a government misuse of a technology if there is no public scrutiny of the science and its application. It sounds like DOE is ready to move in that direction. It's an important focus for keeping the public trust. It's part of responsible science.

Innovation and Intellectual Property

Two questions need attention.

1. Do we know whether intellectual property helps or hinders genomic innovation? There is no answer yet. Drew Endy's characterization of the literature is not far from the truth: we analyze one feature of the IP system after another and say "Here's what's wrong with it," but there's a set of problems in the real world that all those pieces of IP would have been in instituted to solve. Copyrights and patents do real work in the real world—and while we continue to say there's something wrong with the patent system, we don't come up with a substitute. And genomics has hardly a desert for innovation, more like a fountain. Is this despite or because of 38,000 DNA patents? We need to move beyond this easy critique of what's wrong and think about concrete things that could be done to improve it.

It is not likely that the patent system will be restructured any time soon. Patent law will be out there, so *sui generis* kinds of solutions to the problems caused by patents in these areas of rapidly developing science are not going to be found by creating a completely new form of IP. It would be much more productive to turn our attention to how IP is used and assume that the current forms of IP will be pursued vigorously. The 38,000 DNA-based issued patents in the United States are evidence that someone is willing to pay for IP in genetics. Much of the policy is about how people use it, what the rules are when you use someone else's invention. One deep problem here is that it's impossible to study because much of the information is buried. Much of it is kept secret, except when a lawsuit goes to public litigation. If I were focusing my attention on policies, I would be trying to get more information into the open; it's a completely nontransparent system. Even universities who are using Federal dollars to create Federally funded inventions and licensing them under Bayh-Dole don't have to report to their

project managers at NIH how they use their patents. That's why we did the survey through Georgetown to figure out what universities are doing with their DNA patents. Grantees do report on their patenting and licensing to a part of NIH, but it doesn't go the people who are making decisions about funding, to the NIH technology licensing office, or to those responsible for information-sharing policy concerning grantees and contractors. It goes to a database that's handled by a different staff. I believe public accountability should follow public research dollars: open up the system so we know what people are doing with IP created by federal spending. I would also argue this for privately funded inventions, but that's a different matter and a weaker argument.

2. What happens when the science is foreseeably valuable in the commercial sense? (NIH will resonate with this; conflict of interest has been a policy priority in the intramural program there for the last 2 years.) Commercial value is apparent in many areas of molecular biology and will be for both nanoscience and synthetic genomics. It's problematic that the issue has been framed as conflict of interest because that framing reduces it down to the level of individual scientists making decisions about how they behave, and it's not a promising way to solve these problems. Disclosing company affiliations doesn't necessarily change behavior (nor should it necessarily do so). Nor is "buyer beware" the only way to handle this. I don't think disclosure will solve most of the problems; the problems are system bias. Why do we really care about such conflicts? Well, when you're putting drugs or biologics into peoples' bodies, you want to know that the people volunteering to participate in those studies have all the information they need to know about whether something is likely to be safe and effective. It's not about whether a researcher has a conflict of interest, it's about whether they have provided to the research subjects all the information they need to know prior to volunteering in a study. If the researcher has a stake in the outcome, then trust in the system is reduced. Indeed, we have a problem even it just means researchers are more blind to safety concerns, publish only positive trial results, or design trials that miss safety concerns or bias towards finding efficacy. Conflict of interest plays into that if somebody in the network of science favors some information becoming public while other information remains in oblivion. The deep problem is system bias that is slanted toward finding positive outcomes for new technologies and neglectful of safety concerns or negative results.

That's where we've been getting in trouble in clinical trials—a system bias in favor of reporting results that favor the folks funding the research in the first place. Can we design a study to produce the results we want? To some extent. We are all better off if we have a system that produces valid information. Do we need information about how many tests have been done on a certain technology? Yes, we need to have safety information on that technology, and we don't have a system that produces that information. Again, we need to push for transparency and for thinking about these issues of high-stakes science where there's a lot of money to be made at the back end (this is a good thing—lots of drugs have made it to the market and are saving lives). At the same time, the public is right to be suspicious about the system if it pushes results that curry favor with the folks funding it. We need to come up with a system that works better and it won't be by disclosing of interest, although that may be a necessary step. The only solutions proposed thus far have tended to be in the form of disclosure. But we really need serious thinking about system bias.

Questions and Discussion

Q: Another category of dual use is economic. Looking back at the history of Internet development, we observe today that maybe the largest category of direct Internet commerce is porn. There's been some discussion along the way about whether to put that into a particular category for the Internet and discussions of taxation of that and so on. When we look at synthetic biology and think who might be the earliest adopters, it's easy to say that the illegal drug industry—sophisticated in many regards and with long supply chains that are frequently disrupted—could be an early adopter if it could find ways to have small-scale distributed production to develop many new products and deploy those products in markets at the garage-biology level rather than supply chains from Afghanistan. I wonder what your reactions are to that and how one might think about it from a policy perspective.

A: I don't know what to think about that. If you can think of a scenario where these technologies would be used for that purpose—and it seems plausible—it's time to worry.

Mildred Cho: There is another thing along those lines, in terms of safety; I'm concerned about the possibility of a molecular kudzu, well-intentioned uses that go awry. Something is released into the environment that can't be controlled.

A: There are lots of ways to handle that. We've had a 3-decade debate about testing new technologies, mostly in agbiotech and livestock applications. There are some really interesting, controversial areas there. In North Carolina, we're having an active debate about GM conifer trees that last for many decades and spread their pollen over huge geographic areas. Most current policy focuses on restricting or circumscribing field testing for plants whose pollen goes short distances and that have relatively short lives. The game is different with living things that last longer than humans and spread their gametes for hundreds of miles. So we're already having these debates at least in this context. We kind of understand GM food and crop plants, but as soon as you modify a pine tree, the potential for growing uncontrollably is real. Yet you want to encourage the development of new stocks—so it's a tough question that folks are beginning to struggle with. It's helpful that the biologists are trying to engage others in this debate.

Mark Alper: I thought I understood your category of government misuse as dual use until you made the anthrax example.

A: I wasn't clear. I did mean to refer to governments or individuals within government research establishments pursuing deliberate actions that are destructive. All we can say about the anthrax story is that at some point the thing used badly was part of the biodefense-bioweapons establishment. We don't know if government workers did it. I sure hope it wasn't a result of systematic government action.

Dan Drell: A comment about Mildred's point. There's a distinction between the introduction of genes and whole organisms that raises the question of where to draw the line: one gene, one operon, one chromosome, more? When might this become unsafe?

Bob: So many things are in play in connection with self-replicating organisms, you have containment strategies that could be physical or biological and are usually both. If you're only changing a bit of the genome, maybe you can feel confident enough that it's not that big a deal; well, it depends on which part you're changing and what it does. And that in turn can depend on deep knowledge of biology, and it may be quite difficult to create bright lines, yet law and regulation do best with bright lines. So I'm not sure, I haven't thought it through.

One other point to make—one way of thinking about ELSI programs is that they are freestanding research enterprises and there is value in that. Our Center for Genome Ethics, Law & Policy is not free-standing. It is one of six centers that together comprise an overall Institute for Genome Sciences & Policy at Duke. That structural fact matters in how we work. The most significant thing for an ELSI component of our genome institute is not always its research—although it is prestigious to get an ELSI grant for Duke—and we're creating new ideas and data. But often our value comes from giving advice in an operational sense. Every week I go to a meeting with other centers who are doing science and making decisions about how to shape and frame that science. How to think about creating a repository, how to do population genetics and pharmacogenetics studies--these and other discussions take place, and having someone think about the ELSI of doing this science and how it will be applied or how the world will react affects how decisions are made and which way those decisions go.

DOE supports institutions that are pretty large and hierarchically organized—that may be a frame for an ELSI program for DOE that would be advisory to line authority—an assemblage of people thinking about ELSI issues as decisions are being made. I don't know if it will work or if it will matter, but it's colored the way I think about how a policy and law component to any scientific enterprise should be—thinking about a set of issues and bringing those to the table in real time. It's different from thinking about ELSI as a purely research enterprise. Also, I think research is important, but it is not the only way to go about this business. What may be the most important thing is influencing the decisions at the margin as they are being made.

How Might We Respond to the Issues Discussed?

Dan: Now we'll raise some possible models for how the Office of Science might institute a capacity to deal with the issues we've talked about in the context of what Ray Orbach said—integrating societal implications into the early stages of a project.

"Benchside Consultation Service" Model

Mildred Cho (Stanford U.)

The program at Stanford is based loosely on the idea of the bedside consultation service used in hospitals. Ours is called the benchside ethical consultation service. It's a service for bench and clinical researchers that is proactive and intended to provide a rapid response. The key features are that it's

- Proactive, allowing researchers to raise issues before the fact.
- Integrative
- Anticipative
- Educational in the sense that it educates researchers and consultants.

The short-term goal is to provide real-time advice to answer the specific questions asked by these researchers to the extent that is possible. The longer-term goal is to create a mechanism for trust building among scientists so they can learn to trust others to talk helpfully and constructively about issues outside their own community. This is just one facet of other programs that could be instituted in parallel to create a forum for facilitating dialogue in a safe environment for scientists.

The service includes a multidisciplinary team consisting of a core that includes an ethicist (Cho), a philosopher, and someone from the law school, along with a larger set of consultants at Stanford. This team can receive queries by e-mail, phone, or in person; they try to provide a response in 48 hours even if it's not complete. All these consultations are initiated by scientists. We hope that at the end we can suggest some kind of answer and that it can be generalized to help others outside that laboratory.

Since November when we started a pilot test of this, we've done eight consultations at a variety of stages in the research process. These range from "we're thinking about doing this research" to "we have funding and are halfway through our study and someone died and we wonder if we should have done something to prevent that." In looking at this over time, we'll see if the consultations change. We're hoping they will come to us earlier and earlier in the research-design process. It would be nice if they came before funding, so we could build this service into the proposal.

We've done consultations on a range of things: mostly human-subject research, some genomics, and other things. I'll talk about some outcomes thus far. In several cases we can see suggestions of trends in the kinds of issues that come up. Already in eight cases, some themes come out: One topic is the incidental findings of research—findings not anticipated by the researchers. A question that arises is whether those findings should be reported to the research group or the participants. Another topic is conflict of interest in all different forms.

Some consultations have led to institutional policies being developed about issues not anticipated before; some were administrative, such as clarifying which kinds of researchers fall under regulations, or other conflicts of interest. Some issues will lead to workshops like this in which groups outside Stanford will be brought in to address topics with bigger implications than can be addressed in 48 hours.

Examples of more to come out since November (2005): the integration of this kind of consultation service into large grant proposals. Proposals for two major grants have gone out that include support for ethics consultation services alongside research core facilities like bioinformatics and biostatistics. This indicates a shift in thinking towards integrating these activities into the research process. We've also done some consultations for funding agencies with questions about whether to fund some research projects because of ethical questions. We were

also approached by some companies in the private sector with questions about how or whether to proceed with new or early research.

We are just coming to end of a 6-month pilot phase, but we are already seeing that this kind of service will be useful for generating dialogue and providing this service to communities. Over the next few years we'll be tracking these cases, following outcomes and asking whether this leads to researchers changing what they do. If so, how? How often do they ignore advice? How is it presented in publications? How do researchers feel about these interactions—were they helpful? There are other questions as well.

Asilomar Model

Bob Friedman (J. Craig Venter Inst.)

My talk is labeled "Asilomar model," so I'll explain that term. A meeting was held at the Asilomar conference center at Pacific Grove, California, in 1975 with about 140 guests, many from Europe, some carefully chosen members of the press, and some others. The purpose was to respond to a self-imposed voluntary moratorium on recombinant DNA research that was originally proposed by a National Academy of Sciences committee. The meeting attendees wanted to discuss whether the moratorium should be lifted. There was a strong incentive for the science community to participate: they wanted to use a very powerful new research tool. Paul Berg, David Baltimore, and Sydney Brenner were on one side with James Watson and Joshua Lederberg on the other. (There's a great *Rolling Stone* article about the workshop that came out shortly after the meeting.) The meeting ended up recommending lifting of the moratorium with conditions: a set of progressively more stringent lab procedures to follow as the experiments increased in potential risk—the precursor to our current Level 1-4 biosafety system now. The meeting proposed a very novel safety feature: organisms used in experiments must be biologically incapable of living outside the lab. The attendees also proposed education and later reassessment of conditions. So, some stringent controls were put in place and were lifted as we learned more to help us understand about the new technology. So it was a wonderful outcome, often posed as a self-governance example.

There may be another perspective on this—it was a visible indication of the introspection and concern by the scientific community, their concern for what the public and policymakers thought. Many of the sentiments behind this were due to Congress being ready and willing to legislate the use of this new technology. The perspective I like is that it was a wonderful example of participation by the scientific community in governance of research, a willingness to hear the concerns of other segments of society. The *Rolling Stone* article talked about some other attendees; one of the most influential was a lawyer who talked about potential liability concerns, which came as a surprise to many present. When I think of Asilomar, a lesson I like is the notion of participation by the scientific community along with others in the actual conduct and governance of research.

There's another dimension that's useful to explore. The moratorium was proposed by a smaller group, a National Research Council panel, which is a traditional route used by the scientific community to work at that time—a small and elite group. This is the first example of "policy by hot tub" within a scientific community. Bring lots of folks together with lots of perspectives in a nice environment. The meeting was very controlled by a small elite group (about 140 people were present), but the openness of the dialogue with others is a good dimension to capture again. Policy, governance by a small group, consideration of ELSI in a larger group.

Bob Cook-Deegan talked of another dimension that is important to this discussion: the research aspect, or dealing with real-time problems as they occur. Asilomar was a response to a moratorium, a problem faced by the scientific community. Another real-time problem was Congress wanting to get in there. That balance of mobilizing and dealing with urgent issues is important for an ELSI program to keep in mind.

Other experiments are out there—Bob also talked about the issue of GM conifers. Knowles and I participate in a small struggling nonprofit—the Institute for Forest Biotechnology—that brings together industry, government, academics, and public interest groups to try to look at what may or may not evolve into a new use of biotech. It's really at the edge, on the horizon. There are strong similarities to the Asilomar model. The added twist on that model is that we do it repeatedly.

One other thing: Mildred Cho, Bob Cook-Deegan, and we at the Venter Institute are starting to see research institutes putting small policy groups inside the fold. This is the next logical extension of making policy—bring the outsiders inside the fence and continue the dialogue on a real-time basis.

ELSI Model

Eric Juengst (Case Western Reserve U.)

Dan Drell and I were the first two program officers for Human Genome Program ELSI. It started when Watson was asked by a reporter about whether he was concerned about the societal issues that the Office of Technology Assessment and National Research Council reports had identified. He said of course and that about 3% of the budget would be used to address them. NIH had to jump on this and established an extramural grant-making program over the next 5 years. There was a lot of uncertainty about what the program should be, but by the end of 1995 it settled into a recognizable model which I call the "UnCommission." As opposed to a blue ribbon task force doing "top-down" policy formulation and producing task-oriented responses to specific issues, what came out of this was a research program designed to build ("bottom up") a capacity in this field. The aim was to build a stable community of researchers who would take these on for a career and would stand ready to respond to urgent issues as they came along but would also be a stable resource for society to draw on (including researchers).

The "UnCommission" was characterized by the following attributes:

- A focus on cultivating a stable community of independent researchers and policy experts who speak the language, take the issues as their vocation, are prepared for the next surprise, and will train the next generation.
- Building the capability to seek out and plug into the variety of policy "receptor sites" (i.e., create a sustainable "social immune system" rather than a series of "magic social bullets").

This is a model DOE could take. Put resources towards generating a field of people interested in the issues of synthetic biology and nanotechnololgy. It would do the academic things of looking after its progeny to raise a generation of young researchers who would stick with these issues and create a field that would be variegated and that could be plugged into a variety of receptor sites (i.e., "customers" for its output). To frame it in the most positive way, the goal of this model is to build a sustainable social immune system ready to react to challenges rather than social antibiotics or magic bullets aimed at curing the next specific infection that comes along.

There are tradeoffs to the UnCommission concept:

Among the cons: It is not task oriented (it can't hammer out federal legislation against genetic discrimination in an afternoon), it could be expensive, it could be hard to control, and it could be hard to measure its success. ["Beware becoming broad and squishy," F. Collins admonished prospective applicants for research centers in 1996.]

Among the pros: It could be long-term, it could be self-perpetuating, it could be infectious (others could pick up on this idea). There is now a flourishing field of ELSI studies in the Science Technology and Society [IS THIS A PROPER NAME?] community unfunded by others, and it could be insidious (insinuating itself into cores of other kinds of institutional centers).

My later talk will cover some lessons learned in getting this model established.

Other Models

Bob Cook-Deegan (Duke U.)

The ELSI created at NIH and replicated at DOE is basically a research program. At NIH a policy office is separate from the extramural grants program; it has a different function that includes liaising with the White House and Congress and responding to the politics of the day. Research is cultivating this also, however, not

necessarily tightly connecting. Places like Stanford, Duke, and Case Western are beginning to evolve a model to think about the implications of science and how it is done. They don't know if it will work because it's a new task. One embodiment of the model: they are trying to create a norm so if someone is thinking about a big, complicated project or one that will involve a lot of people like big clinical trials, they are trying to ensure that ELSI is built into the grant. ELSI scholars are part of research team.

There are societies for thinking about ethics and clinical practice—we don't have an equivalent yet for consultation in research yet except for institutional review boards (called IRBs), but we will have that in 5 years. They will be doing this more systematically.

This is more of a functional statement than a model. I spend about 30% of my time meeting people and making bridges to parts of the university that don't do science and linking them to the science. This includes the business, divinity, law, and engineering schools. It's extremely expensive and unproductive—but not in the long term.

Other Models

Charles Rubin (Duquesne U.)

Ray Orbach tasked us to build ethical issues into science programs the same way that safety issues are built in. I see two problems with this approach:

- The uncertainty problem means that without an ability to foresee accurately where the science and technology are going, we could spend time talking about nonissues and not about the issues that become real.
- There's a limited analogy between being sensitive to ethical issues and sensitive to safety issues. Safety is a habit of mind that involves finding *solutions* to finite problems. Being sensitive to ethical issues involves a willingness to deal with contentious and perennial *questions*.

Precisely because of such difficulties, I was attracted yesterday by the discussions of developing trust and building relationships (e.g., Mildred Cho's talk) as opposed to trying somehow to formalize sensitivity to ethical issues. But even here I see challenges, including:

- We live in a large society made up of highly diverse publics, making it difficult to build trustworthy relationships.
- Our political institutions, which form so much of the basis for public discussion of issues, aren't built on trust. Even in the academy, we are accustomed to dealing with adversarial relationships. Trust can grow out of such structures, but it does not have to. We put so much weight on transparency and accountability to constrain decision makers just because we don't assume trust.

The persistence of contentious ethical questions combines with the difficulty of creating trust to create a formidable challenge with no easy solution. Those working in groundbreaking areas of science and technology need to work in the open, being seen by the relevant publics to be routinely reflective, self-critical, and self-aware of the consequences of the research that's being undertaken. It's not asking a lot of people to look at their work to see how it could be misused. But another part of being reflective has to do with more difficult questions of values or framing—why are we doing what were doing in the first place? What good are we trying to achieve?

What incentives can DOE provide that will promote this reflection and self-criticism? Based on my experience, I think two kinds of conferences could promote it:

1. Kenyon Public Affairs Conference Center model. Such conferences bring together recognized and up-and-coming experts in a field to discuss timely and familiar topics, making sure to allow for diversity of views so that the experts will argue with each other. The papers that they are discussing are then revised and published for use in classrooms or maybe by an interested lay audience. The conferences themselves are "off the record" and only semi-public to encourage candid discussion, but you could bring in a select audience.

2. Liberty Fund model. This kind of conference can bring together a diverse group of practitioners, academics, poets, media, and artists to talk about topics, issues, or works that take them more or less outside of their usual areas. The focus does not even have to be something obviously timely. The point is rather that everyone has the same starting point in struggling together with perennial issues or classic texts. Rather than a physical product, this conference aims at forming networks and relationships.

One drawback of what I'm suggesting is that conferences are routine and therefore may create limited incentives. Also, it's a very modest approach, which may make it less interesting to a big-bucks outfit like DOE. Yet the opportunity to offer such conferences may bring into the field people who cannot compete for million-dollar grants but can for a $50,000 conference grant. This suggestion won't result in reaching all publics in a large-scale deliberative effort, but frankly I think that hopes along those lines are easily overblown. Finally, it doesn't even attempt to solve bureaucratic or regulatory issues in relation to new procedures and processes. But it's an approach that can help build capacity and willingness for undertaking serious reflection on the moral questions that new technologies are creating.

Discussion About Session

Tom Vogt: Some of these models reduce our accessibility for doing this kind of work when we need to reach out to as many publics as there are, especially to those who are critical of our work. We defeat ourselves if we try to graft onto a classic academic model like little conferences.

Ray Gesteland: A comment on the Asilomar model. This public self-flagellation also had a feeding frenzy to it. It resulted in a one-to-two year setback of that field. There wasn't a quiet opportunity to reach out to the microbial community; instead, the frenzy took over.

Question to Mildred Cho: The benchside model is a great innovation. How do you aspire to reach the nonself-selected group?

Cho: It's a weakness of our model. Our intention is to grow the self-selected group, but all we've done to date is put a more formal structure to what already was going on. Several have come because of former consultations with our group. We want to create a space for scientists to look at values. This is drummed out of us in the training process.

Bob Cook-Deegan: Another thing to do in terms of the outliers is to change the policies—it's happening at a lot at other places in the wake of NIH conflict-of-interest problems. Anther thing, when you're sitting in on decisions when they are being made, you have some input.

Mildred Cho: A comment on Ray Gesteland's comment about Asilomar. I left University of Pennsylvania just before the Jesse Gelsinger story broke. Human genome research was suspended for at least a year there, and part of the lesson from that is that the actual issues that arose as a result of that case don't highlight where some of the breakdowns occurred. There were issues that were not brought up in the court case, which focused on informed consent. Informed consent was the tip of the iceberg. Along the way there was a breakdown of communication between the protocol researchers and others, including not taking advice that had been given to them. That advice had focused on basic issues of study design, of what research to pursue, and what not to do. A lot of these processes are not known outside the community. Part of the problem at U. Penn. was their pursuing a research protocol in an area that seemed promising from a scientific point of view but inappropriate in terms of what disease should have been chosen. This was discussed but not followed through.

Bob Friedman: I'm going to withdraw the "policy by hot tub" analogy. My point was to start with a small elite group of scientists alone and then open up the process to our 21st Century version of Asilomar where we are much more open. After-the-meeting discussions are important.

Lessons Learned from HGP

A Personal Perspective

Dan Drell (DOE)

Since 1990, the DOE HGP budget has been about $1.2B (to date), with 3% of the genome operating budget consistently set aside for ELSI (about $36.1M). At NIH, it was first 3% and later 5%. A key question was not whether ELSI products were good or bad (they were mostly good) but whether or not they influenced genome science. I think the answer has largely been no.

What ELSI did well

- Sponsored good academic research
- Supported a considerable amount of education of groups
- Stimulated a cohort of scholars to enter the field of bioethics
- Expanded the discipline of medical ethics to include genomics
- Shielded the HGP science program from Congressional (and some public) criticism

What ELSI didn't do well

- Integrate with ongoing HGP science
- Inculcate a sensitivity to ELSI in most HGP scientists
- Define its appropriate role vis-à-vis policy formation (ambitions of some in early ELSI were politically unrealistic—policy is made by Congress and the Executive Branch and its agencies)
- Justify itself in positive terms as being of value to the HGP
- Influence the direction, pace, or public perception of the HGP
- Change the perception of ELSI as inhibitory to science rather than contributory

ELSI did great work but did not have much impact on HGP progress, especially after 1996 when it became a "race." None of this means ELSI was a bad idea. It was an experiment that needs work. It missed some opportunities.

What ISIS needs to do

- Define how studying societal implications can benefit the science
- Make the case to DOE-supported scientists that they need to take it seriously
- Look at issues down the road (ES&H being looked at already)
- Invite peer-reviewable studies of the implications of societal issues but link these to ongoing science in more tangible ways
- Build a collaborative environment among scientists

In my personal view, there should not be a set aside for ELSI.

A quote from Ann Finkbeiner's *The Jasons* (2006):

"This is where the science advisor comes in, to start the debate and then to inform it; to tell the government and the public about those applications and their potential benefits and threats; to keep the public debate grounded in fact; and to keep it within the bounds of reality."

Another Personal Perspective

Eric Juengst (DOE)

ELSI Program Timeline

1987–88: Office of Technology Assessment and National Research Council reports. Congressional hearings.

1989: Watson commits 3% in response to media question.

1989: NIH-DOE working group on ELSI. A nine-point agenda: research and policy translation.

1990: ELSI program announced. Open solicitation for peer-reviewed extramural research.

1990: Bush-beating workshops held to get grantees.

1990: NIH-DOE ELSI working group began.

1991–92: Privacy task force (DOE), Institute of Medicine Committee (NIH), Insurance Task Force (NIH-DOE).

1995: Joint NIH-DOE ELSI committee to evaluate the ELSI program (Spence/Rothstein).

2000: ELSI research planning and evaluation group (Walters).

2005: ELSI Research Advisors (Burke).

Having been in ELSI for 12 years, I left in 1994. I notice the passion in Dan's voice that comes from being in the trenches. I'd like to talk about how I see the evolution of this model, which I still like. I am not sure we had conflicting models in the discussions as much as just different slices in time for different fields.

Before the HGP got started, as its scientific merits were being debated, there were in the feasibility studies the traditional last chapters for ELSI. It was unclear whose responsibility it was until Watson spontaneously responded to the reporter. NIH stood behind it, and DOE got browbeaten into it at the hearings, according to Bob Cook-Deegan.

The ELSI program started in 1989 with the launch of the new National Center for Human Genome Research at NIH. The working group they put together for this commitment to spend research funding on ELSI was one of those elite groups, but it was interdisciplinary and included known critics of HGP like Jon Beckwith (Harvard). The Working Group generated a research agenda and launched a program with a program announcement. That's when I came in. Interestingly, I worked with someone at the University of Pennsylvania who predicted that the HGP was on a collision course with the religious right—which never happened. Instead, the collisions down the road have been on the left, with people having disabilities and green parties.

Shortly into ELSI, there was confusion about what it would do for genomics. Congress responded so warmly to Watson that he felt it was urgent to quickly get some policy solutions to the urgent issues of the day out there in a quick-turnaround way. Well, who was going to do this - not the first round of grantees barely getting research together yet?

That community of grantees was being created by the kinds of meetings that have been suggested, people who would beat the bushes for potential scholars to entice people into the field.

Who was going to do policy work? This fell to the same planning group, the ELSI Working Group that advised the grant programs. They were tasked to identify the most urgent areas. Three high-priority areas: privacy of personal genetic information, clinical integration of genetic tests, and fairness issues of access to benefits and antidiscrimination. All these are interesting but far downstream from mapping and sequencing, by intention. They took it for granted that the HGP was a good thing, they just wanted to make it happen in a socially optimal way. So their view was naturally downstream when genome knowledge became applicable—it wasn't designed to have an impact on the science. That raised an interesting tension within the genomics community and the source of our problems in not being well integrated into the genomics world. Scientists said these

weren't genome issues, another agency should be paying for this—these are worries about downstream effects. "We've had enough of this Hasting Center stuff," said a quote from *Time* magazine early in the HGP.

They were striving to live up to instructions to be a policy operation and spun out "magic bullets" -- task forces—on various high-priority areas. These were too little and too ineffective. Reports said that the ELSI program had no conduit into the policy process and was just spinning its wheels and putting books on the shelves. This is ironic since, from a loose group of grantees and pro bono advisors, it did produce model legislation for policy, and it did stimulate the advisory committee on gene testing. The insurance task force was picked up at the highest levels by Hilary Clinton. Oh, well.

There is the question of how to evaluate ELSI's impact on policy. Watson said his criterion for ELSI success was if someone was complaining to him in 15 years that it was all a waste because we spent all that money on ELSI and nothing bad ever happened. We got out in front of it, it was preventive. So it should be to ELSI's credit that there's no evidence of genetic discrimination in insurance. So was it due to their proactive efforts? Who knows? How long in the future can we live up to the standard of "nothing happening" for the program to continue to be considered a success?

Evaluating a prevention program:

- Causation
- Controls
- Endurance

The ELSI program has had a series of 5-year checkups about the connection between the research field and the policy process. In 1995 another committee was formed to look at the program, and they decided on the UnCommission model. Let's focus on the research and export evidence-based policy options to appropriate receptor sites.

Focus on research; export policy translation:

- Technical assistance and cross-disciplinary training
- Cancer genetic consortium, stored tissue research
- Secretary's Advisory Committee on Genetic Testing (SACGT), National Coalition for Health and Professional Education in Genetics (NCHPEG), and Genetic Alliance

They were able to produce focused research (e.g., looking at predictive testing to inform professional policy).

In 2000, the ELSI lens began to drift upstream into research process. The ELSI Research Planning and Evaluation Group (LeRoy Walters, chair) started first with the task of thinking about biobanking and stored tissue research. In post-HGP, all the research began to involve human communities. What was needed was a research community building for scope, synergy, and stability to look at issues such as:

- Genetic variation consortium, hemachromatosis consortium
- HapMap integration

This brought the focus of ELSI into the research stream itself. In post-HGP, the uncomfortable process now of the ELSI folks and genome scientists working out a relationship is to build a next phase in which millions of personal genomes are stored on the Web. Now the rubber is hitting the road as far as the ELSI-genomics relationship is concerned. The last review of the program in 2005 pointed to this as the theme for the next period.

ELSI in 2006

The UnCommission didn't do a bad job of plugging into the receptor sites; most states do have some kind of law against genetic discrimination, and there's a federal law in the process. Our social scientists are reporting that the media and the public show a more nuanced understanding of genomic information (Conrad/Condit) after 15 years of education efforts. The other side of that is they are more skeptical and less excited about genome science.

Clinical genetic testing standards of care are evolving as a result of ELSI research.

The human subjects research landscape in genetics has been transformed partly in response to ELSI work and scandals. We've been paid the compliment of having critics on both sides. The social critics of science are saying, "Just as we suspected the ELSI program has just been a shill for Big Genomics and has paved the way for the rollout of HGP and post-genomic initiatives. Look at how they are facilitating the international HapMap by recruiting communities and talking to them." We've also been accused of "constricting the pipeline" of research and inhibiting the translation into applications (suggesting that we have a big influence over the research behemoth, which is flattering but not so).

The field is blooming internationally. ESLA in Europe is their equivalent to our ELSI. I'm going to a workshop about other countries funding this kind of work. So the spread of these ideas has begun to address those offshore issues that come up repeatedly in these areas (need others besides the United States to come up with policies).

Pros and cons are still there (see his earlier talk).

It does build the capacity to get you to the stage where genomics is now, where it makes sense to think about a benchside ethics consultation. There are people out there that you can turn to. At the beginning of HGP it would have been a strange and unworkable idea. We needed the time to integrate communities and gather the evidence and experience to offer this service.

Lessons for nanoscience from ELSI:

- Create the "cultural architecture" of moral imagination and interdisciplinary collaboration earlier. Nanoscience seems to be off to a great start.
- Experiment more with funding mechanisms. The NIH ELSI program struggled to fit NIH mechanisms. To fit interdisciplinary research and policy activism into those mechanisms was (and still is) awkward. An idea someone gave to the ELSI program early on: have an essay contest. Take $100,000 (a cheap RO1) and have five $20,000 prizes. Essays should be blue-sky forecasting of what the nanoscience and synthetic genome issues might be. Of course, you'd keep all the entries.

I'm interested in Dan's reference to *Prey* as a bete noir for the nano community. So why doesn't *Jurassic Park* generate angst for the synthetic biology community? He says both will fade from the popular imagination.

Discussion of Perspectives

Dan Drell: If you were designing this from ground up, what would you do differently?

Eric Juengst: Finding ways to get into it at the CD0 level is crucial. Start the socialization process and build the community.

Dan Drell: How do you handle assessment questions in the light of the Government Performance and Results Act (GPRA)? How do you measure ELSI?

Eric Juengst: You could trace the etiologies of those social events and point to the role that ELSI-funded research has played in it. This is an ongoing project. It's not an easy metric or a standard evaluation tool. It's always an issue.

Jean McEwan from the NIH program: On the one hand it's great that ELSI has spread around the world and into nanoscience. On other hand, I sense that we use the term ELSI without any sense of definition, and it leads to imprecision in thinking about the issues and evaluating the work of an ELSI program, which is just a program within larger ones. It's not all bioethics. It's at least four distinct sets of activities without really thinking critically about how they differ: research, education, policy development, and public and community outreach. There's an inherent tension in establishing ELSI within an agency that is also funding the science, so it's always difficult to define its appropriate role and measure its success. They get accused of squeezing the pipeline or are seen as a shill for the science. This happens when a program is trying to be all things to all people. I was

recently in Japan talking to genomic researchers who are launching biobank projects. They are so proud of putting more than 5% into ELSI. What does this mean in Japan? It's PR for the biobank. It's not my idea of ELSI, but I'm not sure what it is either. We need to get more precise about what it is—research, education, policy dev, PR? There are different measures of success for each.

Bob Cook-Deegan: Integrating into the science is valid but the creation of value is more important for ELSI. *From Chance to Choice* is an example of inherent value—it teaches about eugenics and genetics in the real world. It's probably the most widely used text and was put together by a bunch of philosophers. Another thing: the policy engagement part of the agenda is important. It's hard to measure in quantitative terms, but you can tell the stories. Tease out the stories, and history can do this for you. It would be great to write these stories up. Not many people know about it and there's still interest from the media.

Dan Drell: So it's 2006 and the genome has been sequenced. What would be the difference if there had never been an ELSI program?

Bob Cook-Deegan: Thirty-eight states did something; they are paying attention to the use of genome information by the insurance system. They pushed the momentum of misuse of genetic tests.

Eric Juengst: I gave three examples that rely on a leap of faith like the guys dancing in Central Park to keep away dragons.

Christine Chalk: Lots of people are trying to do things in the ELSI territory, and they are well meaning but not informed about research that's out there. OSTP is looking into conflict of interest now.

Mildred Cho: Back to the question about what if we didn't have ELSI. I'm pretty sure that as a result of community building the fact that a graduate student will call and say, "I have a genomic oscillator in *E coli* and can I come over and talk about ELSI"—this would not have happened. Senior scientists are asking the same things. Questions like this can even be raised in scientific meetings now. It's too limited to think of policy-development impacts as the only benefit from ELSI. Thinking about it as not being grounded in fact is to miss the point. Different things are relevant to different people—we see it in stem call research—issues that are important are not necessarily facts but values. To think about the stem-cell research debate as about abortion also missed the point. IP, ownership, corporate intrusion into science process—all kind of other things that have to do with trust in the science process, these also are issues.

Nigel Cameron: As far as built-in ambiguities are conceerned—that's the way it is. It's not going to work given the kind of agenda coming. Wrapping up of questions forces us to have real questions about to what we want. ELSI is a dry run for what happens next.

Tom Vogt: There's an expectation that ELSI efforts should influence how nanoscience is implemented. Look at the nanotech act in 2003—there's a clear distinction that the center for nanotech preparedness would focus not on academic assessment but on impact (not broad and squishy). Once in awhile we need antibiotics, we can't just pave the way. Have to constrict the pipeline a little sometimes and not just pave the way.

Eric Juengst: I was at a meeting in which this came up: the role of ethics and putting on the brakes. What are the functions of brakes on cars? To allow it to go fast; without them you can't do it.

The Regulatory Environment for Nanoscience and Synthetic Biology: Challenges and Prospects

Dave Bjornstad (ORNL)

This talk discusses the special attributes of nanoscience and technology, synthetic biology, and other emerging fields that may cause unique challenges to the portions of the U.S. regulatory system that seek to protect human safety, health, and the environment. It is divided into two parts, plus a conclusion.

First, I present background on risk-based regulation and how the existing regulatory system, as administered by the Environmental Protection Agency (EPA), the Federal Drug Administration (FDA), and the Occupational Safety and Health Administration (OSHA) are preparing to regulate nanotechnologies, based on the Toxic Substance and Control Act (TOSCA), the Food, Drug, and Cosmetic Act, and the Occupational Safety and Health Act, respectively. EPA, for example, is undertaking preparations through a combination of research, life-cycle case studies, expanded collaborations, and training programs. At the same time, critics are pointing out how current interpretations of rules and procedures may require adjustments. Some feel that new legislation may be required, as in the case of TOSCA, a law that places significant burdens on EPA to justify virtually any controls.

Second, I highlight special attributes of these technologies suggesting that these agencies may also have to undertake significant new responsibilities that could require additional resources.

I argue that four attributes are of special importance and interpret them for nanoscience and technologies:

- Nanoscience and technologies often differ in kind rather than degree from their antecedent technologies. This makes regulation using established relationships from existing regulatory targets (substantial equivalence) less applicable and may require developing data on new targets.
- Nanoscience and technologies, while offering new and perhaps remarkable benefits, will arise from science in progress rather than from settled bodies of knowledge. This means that decisions will be required before a full understanding of risks will be available and may require new approaches to regulatory decision making that are explicitly incremental and subject to review as experience and new data become available.
- Nanoscience and technologies present special challenges to social values, norms, and ways to measure or ascertain them. As a result there may be increased pressures for precaution, even as some groups, for example those funded privately, press on. There may also be less willingness to compromise or experiment in sensitive areas.
- Nanoscience and technologies may present significant external costs. Data from second or further order effects may not flow naturally from the science, and explicit efforts may be required if these data are to be collected.

Finally, I discuss steps that might be taken to address these concerns, while remaining sensitive to the limited resources available to the regulatory process.

As a point of departure, I will relate two stories from my past relevant to the workshop topics.

The Power of Familiarity and Incentives

I came to this business, not as a scientist, but as an economist working at ORNL on policy studies that drew upon the lab's unique databases. There wasn't a policy-analysis division, so they put me in the Health Physics Division, which carried out research that was somewhat related to mine. I was attending a meeting as a young section head when the discussion turned to how the Laboratory's instruments had picked up radiation measurements from a Chinese bomb test. One scientist said that by now there was a little of that in all of us. They thought it interesting and amusing. I also thought it was frightening. There are some similarities to what we're talking about today because with nanoparticles, like radiation, you can't see, taste, or smell them, but you tend to hope there aren't too many of them in you. On the other hand nanotechnologies, like radiation, are diverse so that one can't put them all in one basket. So there are reasons to think that nanotechnologies must be regulated within relevant contexts, contexts that must be limited in number, yet sufficient for policymaking. But while familiarity leads to understanding, it also can lead to a degree of confidence that may be unwarranted and, at the least, unsettling to those with less familiarity.

My other story. Several years ago I managed a task force at DOE that sought to increase the integration of economic principles into DOE decisions. The group was more than a little diverse, relative to their politics and backgrounds, and there was a debate over whether DOE was a policy agency (making decisions that other groups spend money to implement) or a mission agency (doing things such as carrying out programs to develop new technologies). Some assumed that all agencies of government took an active role in making policy, in the

sense that they make decisions that benefit some at the expense of others. By extension some felt that government should take pains to seek out and promote activities—public or private—with net social benefit. Others would accept only the narrowest of roles for government as a gatekeeper in the limiting of some activities and promoting of others. It took me only a short time to realize that each task force member came to express his or her own values (or those of the group they represented). Hence, just as the academic community placed their confidence in analysis, the business community placed its confidence in the marketplace. Common interests aside, it is useful to remember that the various parties to the regulatory process will typically promote their own interests and respond to real incentives as they perceive them.

Traditional Regulatory Practices

Most regulatory bodies that deal with environment, safety, and health (ES&H) adhere to risk-analysis practices when the science and resources lead to clear-cut answers. The current regulatory system is implemented by groups like EPA with considerable input from scientific community, bodies like the National Academy of Science, and the groups to be regulated. Risk analysis generally attempts to establish the cause-and-effect relationships that describe the harm to various receptors from potential exposure to some substance and to track the pathways (between receptor and substance) that lead to actual exposure. Policy can then set standards or other restrictions that reduce exposure or reduce the harm from exposure, such as providing safety mechanisms.

Regulators prefer to have the science clear from cause to effect to pathways. It's a clean and defensible way to make policy. One can then debate the criteria to govern standards, such as an "adequate margin of safety" or a benefit-cost test. The stronger of science, the stronger can be the basis for choosing standards, given criteria.

As it turns out, it is typically not necessary to do science for each and every product of process that is subject to regulation. The way most things are regulated is by drawing analogies to something else, a regulatory approach called substantial equivalence. It means if you've got good science and you understand cause and effects and pathways, you can use the results from one narrow product to regulate a range of related products. This gives regulators some freedom to expend resources on other topics such as emerging products.

In contrast, when the science is inadequate, values become more prominent (for example, the concept of risk governance, which is growing in popularity in Europe). Here the issues might be over whether to undertake new research or production (e.g., bionano technologies), over the willingness to undertake controversial research (e.g., stem cells), or over accepting some risks to gain greater understanding of regulatory needs. The point is that one must have some operational way to deal with poorly understood risks. Options include:

- Accept some risks as a learning process, possibly by relaxing the "substantial" part of substantial equivalence;
- Apply the "precautionary principle." Precaution can imply a lot of different metrics, but it is basically a conservative approach that eschews risks;
- Provide information to those affected, and let them make choices over how to proceed.

To summarize, when the science is strong, choices are easiest and values will typically be less obvious. When problems are more complex and the science less clear, choices are less obvious and reliance on values grows. Some persons' values call for precaution; others' call for moving ahead.

Current Regulatory System

The current regulatory system is a product of evolution based on the accumulation of legislation that addresses specific regulatory issues. The system tends to be fragmented and heterogeneous, which is to say that different agencies could be regulating different aspects of the same targets. The system tends to change incrementally and is conservative in the sense that internal forces oppose broad-based changes or radical responses. The tendency is to fit new topics into the existing framework. This contrasts with academic advice that proposes more sweeping responses and often implies a need for new resources to implement them.

The system is well aware that nanotechnologies are rapidly emerging. EPA will deal with this set of targets principally through the Toxic Substances Control Act (TSCA); FDA will deal with it through the Food, Drug, and Cosmetic Act; and OSHA will use the OSHA Act.

Because EPA has significant responsibilities for nanotechnologies and has begun to address this topic, it makes a good example. TSCA is designed to prevent new chemicals from escaping regulatory attention, though it does not seek to slow the development or use of new chemical products. EPA convened a working group over a year ago to study how TSCA could be applied to nanotechnologies. A draft report is on the Web and is being reviewed (www.epa.gov/osa/nanotech.htm). It says that EPA will accept the challenge of regulating nanosubstances under TSCA. It will also make use of the technologies in support of its mission (e.g., for cleanup methods). Because EPA follows a risk-analyses model, they will initiate case studies and collaborate with other agencies as well.

FDA and OSHA also are beginning to address nanotechnologies in the areas of drugs, cosmetics, and the workplace, but at this writing they are not quite as far along as EPA. In general, regulators are not neglecting this topic. They have an established starting point and a path forward. Naturally, affected parties and critics are watching carefully.

On the other hand, critics have cited TSCA for a number of weaknesses. In particular, the law places a good deal of the burden of proof for required regulation on EPA. It requires EPA to produce evidence of an unreasonable risk to delay production and provides standards that tend to make it more difficult for EPA to defend its positions than do other laws, such as those for clean air and water. It exempts small batches of new products and generally seeks to reduce regulatory burdens. Some have called for new legislation to target this law more directly at nanotechnology attributes.

Challenges to Regulatory Practices

In my view, a number of attributes possessed by nanotechnologies and other emerging technologies pose particular regulatory challenges. I group these into four categories.

First, many impacts due to nanotechnologies and their products are related to scale, with the result that the relationship between a nanomaterial and its bulk counterpart is different in kind rather than degree. This means one cannot apply existing regulations on, for example, bulk carbon to nanocarbon materials. Differences in kind mean that substantial equivalence may not be valid until the knowledgebase grows. To the extent that a great deal of regulation now relies on substantial equivalence, the growth of nanotechnologies implies either a type of learning by doing or an expansion of resources for specific research to establish new equivalence relationships. More broadly, many other advanced technologies are also different in kind from their predecessors.

Second, nanotechnologies and other advanced technologies typically arise from science in progress rather than settled bodies of knowledge, with several implications. Understanding how and to what degree the products of nanotechnology have negative impacts on targets may emerge slowly, while decisions regarding precautions in production, use, and disposal may be required sooner. When databases are inadequate, scientists may not agree on impacts. As an example, life-cycle effects may be poorly understood. Closely related is the degree to which impacts may be irreversible. When we reach the point that there is a "little of that in all of us," it may be too late to correct deficiencies.

One response to science in progress is a sequential regulation process, sometimes called adaptive regulation. To an extent this practice is already applied in drug trials; we use current knowledge to ground initial standards, but we still keep track of the impacts once drugs are in widespread use. If negative impacts arise, drugs may be withdrawn. Unfortunately, revising past decisions can be costly. It can also prove troublesome if previously unidentified irreversibilities arise.

Third, nanotechnologies and other advanced technologies can present special challenges to values, norms, and the means for explicating or measuring them. For example, values over unfamiliar products may be poorly formed (e.g., What's a "living machine?" What does it mean to inject them into one's body?). Similarly, values over unfamiliar risks may be poorly formed. We have yet to resolve the topic of very small probabilities of very large risks. Should we take expected values or should we apply additional precautions?

Value conflicts and challenges to norms militate against greater reliance on value-based decision making. Challenges include how to ascertain new values, for example, by using opinion polls, developing ways to capture

revealed preferences, and stimulating public discourse. It might be good to develop better methods for addressing value-laden choices and the discipline to avoid making the debate one of science vs religion. Finally, education might best target the formation of public opinion, rather than focusing on "truth telling."

All these lead to a tendency toward precaution.

Finally, nanotechnology and other advanced technologies may present significant external costs and benefits. Most technologies have some external costs, but these may different, and they may be misunderstood. As an example, early critiques of nanotechnologies raised issues of replication run amuck. Today, this is understood to be a distant problem at worst and likely no problem at all. On the other hand, data on second- and third-order effects may not flow naturally from the science—as in the case of "unknown unknowns." We may need to take care to search them out specifically. Often, there is pressure to apply decisions concerning one topic to other topics, a sort of substantial equivalence.

We have rejected the creation of new humanoid species through cloning, but in the United States at least, have embraced the creation of new crops via hybrid processes. What about new species of crops, grasses, trees, or animals via biotechnology? California, for example, considered and rejected the importation of novelty fish that glowed in the dark, due to concerns over accidental release and cross-breeding. Designer trees, optimized fort lumber production, have raised some eyebrows. A number of European countries appear to have rejected genetically modified foods out of a general concern for food quality rather than based on specific evidence.

Summary

When the science is weakest, the regulatory system is forced to place greater reliance on values. Unfortunately, in the most important cases, public values are often not well formed. There are opportunities to gain knowledge through heuristic learning, but the costs of doing so are poorly understood. One potential cost is increased pressure toward unjustified precaution.

So, how to proceed? Candidate steps might include the following:

- Refocus the regulatory mission for greater efficiencies. Devote resources toward a better understanding of which data to collect, which data are analogous to other regulatory targets, and which are not.
- Define equivalency in operational terms. It is widely recognized that analogy by material type may be less valid for nanomaterials, but what basis would be most valid?
- Make the state of knowledge explicit. Methods for making judgments over which data are valid and which are not would help. For the reasons stated above, however, there may be greater challenges to do this with emerging advanced technologies than with those of the past, just as it was easier to pass judgment over the effects on human health of sulfur in the air than over carbon dioxide in the air and its impact on climate change. Nonetheless, standards for vetting the data would be valuable.
- Reconsider regulatory roles and relationships. We should consider changing how players interact in the regulatory process. It may be desirable to increase the already active role of the private sector in regulatory data collection and in other aspects of rule making. Greater self-regulation may be desirable, much as has occurred under OSHA. All this requires creation of incentives to promote behavior consistent with regulatory goals.
- Distinguish degrees of importance and prioritize. It is desirable to defuse trivial concerns, educate uninformed concerns, and elevate critical concerns for public debate.

To close, I have suggested that benefit is to be gained from establishing valid causal relationships that span the range of relevant risks and from discovering the most parsimonious ways to extend them to related products. I have also suggested that when scientific data are inadequate, the regulatory process has greater need of informed values. But, to be more explicit, the regulatory process must always determine just whose values should be included in the process and how they should be weighted, despite the science. This is a task that cannot be delegated. In my opening remarks, I suggested that an overly casual approach to applying science can undermine the process's credibility. I may not want a little of that in me, no matter how comfortable you may be

with your own share in you. In my mind, emotion frequently trumps the data. Likewise, stakeholders speak for themselves and represent their own best interests, no matter how they frame their arguments. Thus, an artificial ranking of scientific criteria over value-driven criteria may be disingenuous and certainly misleading. As the regulatory process seeks efficiency and broadened participation, it would do well to also broaden its understanding of the incentives the various parties face and the consequences that will emerge as they respond to them.

Breakout Groups on Critical Issues in Nanoscience, Synthetic Biology

Charge to group: We want ideas on the issue spaces in synthetic biology and in nanoscience. Also, we want your insights into approaches we might consider to build an ability of the Office of Science to respond to these kinds of issues, keeping in mind that we are looking for something that is "expandable at the margin" (i.e., growable). Assume ES&H-type issues are being addressed. Look a step past that. So, the desired outcomes are a list of topics from which Office of Science can down select for a modest research program and some ideas for a response capability.

Summaries from ISIS Breakout Groups

Group 1

a. Science and values are evolving. Be prepared to adjust ELSI roadmaps.

b. Be a fire-prevention program, not a fire-fighting one.

c. Embed in science and technology studies.

d. Since nano and synthetic technology have security implications, create an ELSI assessment of issues such as the following.
   - Rationales for war, weapons, applicability of treaties
   - Prevention against misuse

e. Analyze state and federal laws and regulations that affect the DOE labs.

f. Analyze what has happened with other technologies and Big Science programs in terms of unintended consequences, how they have been handled, what the public reaction was, and what the policy response was.

g. Encourage interdisciplinary work but also work across science and technology studies so genome ELSI and Nano-ELSI and others get together.

h. Explore questions about operations at DOE labs in terms of environment, health, and safety, and find ways to share with university researchers, FDA, and others.

i. Provide an ELSI agenda for energy research and implementation (e.g., questions of reliability once you get off the grid, concerns about rich or poor and rural or urban).

j. Monitor the hype and review it (such as reviews of all nano reports of NNI).

k. Educate through models like "citizen schools" (scientists, photographers, and others) and projects for high schools.

l. Bring in artists and novelists, predictors of social responses.

m. Do field work in what people want out of the technologies.

n. Talk about what kind of world we want to live in and where we want to go.

o. Look at federal agencies (EPA, FDA, OSHA, USPTO) regulating nano and synthetic biology to see if those technologies raise unique issues and to deal with intellectual-property and dual-use aspects.

p. Create a monitoring program not only of health and environmental issues but also to keep track of changing goals and potential products (note: goal of HGP was clear; here, there are many goals and they are shifting).

q. Explore creation of a social and ethical impact statement for each project.

r. Begin the analysis and social discussion of enhancement and whether we should create life.

s. Review GTL and nano roadmaps from science and technology study perspective.

Group 2

a. Training is needed for news people.
   - The issue is to get a positive message out. Program that gives guidance on how to deal with media, how to get message across, how to frame. This could pay off. Not preaching on public policy but on educating lay community on what science is about. A real obligation.
   - Use the model used at Wisconsin, "Baldwin seminar" for journalists. Journalists come in, ask, go to labs, ask questions. Talked about framing with journalists.
   - One-on-one individual training is important, not necessarily on one topic. Value to both of these activities—one is event driven and the other is not in the heat of the moment.
   - Journalists don't go to routine sources, they go to rolodexes. Create an infrastructure thru formalized meetings. Communicating is important in building relationships with constituents. Groups like EPA do this.

b. Education output from HGP in the long run was very important. Because ELSI was there. An important investment.
   - What specific education is needed? Stanford consultations are being used now as case material in their courses. They hope to have a case book for teaching, with a teacher guide, at the graduate level. Use for NIH-mandated research ethics training. Law schools interested in this also.
   - ELSI is stuff that happens while we're busy doing other things—concerns come up that we don't think of as concerns. That's ELSI. Education, outreach, feedback programs should target broad groups.
   - Educating people about science and ELSI is important; include talk about trust and values. Not just PR.
   - In terms of educating, getting down into lower grades is an investment that will pay off. Send grad students into primary schools. You don't have to get really detailed—at whatever level you target, you decide what part to take, even if you teach the concept that science make advances, gains knowledge, and that it can be used for good or evil.
   - Talk about long-term and short-term communicating strategies; for K through 12, explaining what nanotech is would be a good start. Knowledge provides a framework for processing subsequent knowledge to make an informed judgment.
   - We need to develop information for specific audiences; need to understand what nano does.

c. In addition to educating the public, we also need to say that DOE or NIH should be looking at implications of scientific research. The development of switchgrass for bioenergy—this could have enormous impact. Carbon neutral. This is a different environment from HGP, which focused on how genomic info would affect people's lives. Anyone can identify with it and see the obvious negative impacts. It resonates. Here DOE is trying to say that was good, what's the equivalent for nano and synthetic biology?

d. What are the issues beyond patents or EH&S? There could be economic disruptions with breakthrough technologies. What is the equivalent in nano or synthetic genomics to the genome issue of personal-privacy violations?

e. There could be all sorts of intrusions to our bodies from nanotech. Speculations already are surfacing about brain machine interfacing, stronger muscles. We could be dramatically manipulating the human organism—part of the self-conscious message of nano is that we can manipulate matter with precision and insert them into humans. Bionics.

One possibility: Cochlear implants to treat deafness can raise concerns in communities of disabled people. Nano and synthetic biology may create options for people that didn't exist before. Fifty years from now, say

we have all kinds of nano devices modifying gene activities, will people feel different? There could also be institutional implications—steroids in baseball, polymers in muscle cells, other forms of human enhancement: does this raise institutional responses? Is there a difference between taking Barry Bonds and making him superman,and helping someone to walk? People need to talk about this seriously.

Potential Topics

- Education component:
- PI level: communication with media
- Broad outreach
- Meet with science writers at AAAS
- Identify and discuss ELSI issues with groups—don't dismiss their concerns.
- Use professionals, let PIs back it up
- Economic impacts
- Consider: what does it mean to be human and have a sense of self?

Group 3

a. ISIS needs to be a "fire-prevention" brigade, not so much a "fire-fighting" brigade.

b. An analysis of state and Federal laws and regulations relevant to the DOE laboratories would be valuable; encourage interdisciplinary work, also work across a spectrum of social implications studies.

c. An ELSI agenda for energy research and implementation, including societal and ethical issues, should be defined.

d. The "hype" and excessive promises needs to be monitored.

e. Citizen schools, projects for high school students, artists, and writers, should be initiated to capture their views and predictions.

f. Look at Federal agencies doing regulatory activities, especially for potential "dual use" challenges.

g. The goal of the HGP was very clear; here, the goals are in flux. Perhaps some kind of social and ethical impact statement could be useful.

h. Human enhancement will arise.

Afterword

Jeff Salmon (DOE)

We are at a nexus of science and policy. This raises a series of theoretical questions we are being forced to ask. Not easy since the Office of Science is fundamentally a basic research support organization. Among these questions are:

- Should we do this work (e.g., nanoscience, synthetic genomics)?
- What happens if we are successful, and what does this mean?
- What does the ability to alter human structures and functioning mean for our definitions of "being human?"

Whatever we do, addressing these and other questions will help engender trust.

- How does DOE manage this? Do we become green eyeshade types, trying to count numerically aspects that may not be countable or quantifiable?
- How do the proposed models discussed at this workshop address the DOE desire to achieve real integration of ethics into our work? We not only want to do good things but also want to be seen to be doing good.

One step in the right direction: creating greater self-awareness in our program managers. Others might include, albeit small and in a variety of areas, Kenyan conferences, research studies, and carefully chosen pilot projects.

Ray Orbach likes to solve problems; he doesn't think in terms of small steps. He wants to be bolder than that. When he commits, he acts. So now is an opportune time to take not just steps but bold steps.

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