Gene Therapy Oversight: Lessons for Nanobiotechnology

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Nanotechnology is the "next small thing" in technological innovation. Spanning a range of science and engineering disciplines, nanotechnology will dramatically alter products and processes upon which we currently rely and promises significant advances in technology. Federal agencies taking part in the National Nanotechnology Initiative (NNI) have attempted to articulate a suitable definition for nanotechnology. The NNI definition refers to "[r]esearch and technology development at the atomic scale, molecular or macromolecular levels, in the length scale of approximately 1-100 nanometer range[; creating] and using of structures, devices and systems that have novel properties and functions because of their small size and/or intermediate size[; and the ability] to control or manipulate at the atomic scale."[1] Nanotechnology thus refers to material engineered or altered at the nanoscale, in order to take advantage of unique properties that emerge at that scale.

Nanomedicine is the sub-discipline of nanotechnology striving to use this technology to improve existing therapeutics or create new ones.[2] Scientists are currently developing new ways to fight cancer, for example, by creating nanostructures with unique optical properties that target cancer cells.[3] Clinical trials on human cancer patients using nanoshells have also recently begun.[4] These potentially life-saving techniques capitalize on the unique properties exhibited by nanostructures. But these techniques are also extensions of existing therapies and products that are already regulated: drugs, devices, and biologics, as well as combination products. This raises the pressing question of whether existing oversight frameworks and regulatory approaches are adequate and appropriate for nanomedicine. This is a problem already vexing federal agencies such as the Food and Drug

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Administration (FDA) and Environmental Protection Agency (EPA), scholars and policy makers, and the scientists and business people creating the first generation of products in nanomedicine.

One significant area of medical research in which nanotechnology is making an impact is gene therapy. Gene therapy (more properly called "gene transfer research" because the great bulk of interventions are in the research phase and not yet accepted therapies) is a developmental-stage technique in which genes underlying pathology are repaired or replaced by introducing new genetic material into a cell.[5] There are several different ways to implement gene therapy. A normal gene can be inserted into the genome to replace a nonfunctional gene; an abnormal gene can be swapped for a normal gene through "homologous recombination"; an abnormal gene can be repaired through selective reverse mutation, which returns the gene to its normal function; or a particular gene's regulation (the degree to which the gene is activated) can be altered.[6]

Despite the great promise of gene therapy, researchers have yet to consistently administer gene therapy in humans with a high success rate.[7] Worse, gene therapy research has been accompanied by mortality and morbidity. The death of Jesse Gelsinger in 1999 revealed dangers associated with gene therapy using viral vectors. Gelsinger's death led to the revelation that six other patients had died in gene transfer research — a fact that had not been reported to oversight committees at the National Institutes of Health (NIH).[8] These tragic events demonstrate one of the perils of gene therapy: the carriers of genetic information have typically been viruses, which can cause illness and even death. Other challenges posed by traditional gene therapy include immunogenicity, restricted targeting, production problems, and limited DNA carrying capacity.[9]

Scientists are now using nanotechnology in an effort to develop safer, more effective means for administering gene therapy, specifically nano-engineered viruses as well as non-viral alternatives for gene delivery.[10] The research shows the versatility of nanotechnology in addressing problems posed by traditional gene therapy techniques. The following section describes two categories of nanotechnology gene therapy research: viral gene therapy and non-viral gene therapy.

Gene Therapy Research Involving Nanotechnology

Nanotechnology gene therapy follows one of two distinct research pathways: viral gene therapy and non-viral gene therapy.[11] Viral gene therapy uses viruses as vectors to deliver genetic information to a cell; non-viral gene therapy uses alternatives to viruses to overcome some of the limitations and dangers associated with viral vectors.[12] Researchers are harnessing the potential of nanotechnology and applying it to each protocol for different reasons and with different results, but all are trying to create the "ideal gene delivery system."[13]

Nanotechnology applied to viral gene therapy focuses on engineering particular traits into preexisting viral vector candidates. Such traits include targeting capability and increasing infection efficiency. On the other hand, nanotechnology applied to non-viral gene therapy focuses on developing alternatives to viruses as gene delivery vehicles, to increase safety and efficiency.[14] Viral vectors involve risk that the vector behaves pathogenically and injures the research participant.[15] This risk restricts the dose or amount of virus that can be administered.[16] However, the limited dose of genetically engineered virus can limit the efficiency of viral "uptake" into the affected cells.[17] In addition, viral vectors can undergo "insertional mutagenesis, which limit[s] their use in clinical settings."[18]

Researchers are now striving to develop non-viral alternatives for gene therapy that can overcome the limitations and dangers of viral vectors.[19] Non-viral vectors "offer several advantages [over viral systems], including increased biological safety, low immunogenicity, the ability to deliver large genes, and the possibility of large-scale production at reasonable cost."[20] However, non-viral vectors are not without their own limitations. Non-viral vectors in general do not demonstrate the high transfection efficiencies that viral vectors do,[21] and are subject to enzymatic digestion of plasmid DNA.[22] Researchers are trying to overcome these limitations. The following subsections describe the work of several research groups that are investigating non-viral nano-gene therapy.

INGN 401: Nanoparticle Formulation FUS1

Scientists at the University of Texas M.D. Anderson Cancer Center in Houston have developed a nanoparticle vector for targeted gene delivery of the FUS1 tumor suppressing protein.[23] Dr. Charles Lu and his group have successfully delivered these nanoparticles to lung cancer patients, including three 8-year-olds, in phase 1-2 clinical trials.[24] The gene delivery vehicle is a nanoparticle system using a "plasmid gene expression cassette loaded with DNA that encodes the FUS1 protein. This is wrapped tightly in a form of cholesterol to protect it from the body's defense mechanisms. The nanoparticles accumulate mainly in the lungs, particularly in the tumors, where the genes repeatedly express FUS1 tumor-suppressing proteins."[25] Lu has reported that the only side effect from this treatment so far has been fever, which is addressed with a ste-

roid.[26] M.D. Anderson Cancer Center has licensed the technology to Introgen Therapeutics, Inc., for commercialization of the delivery vector and subsequent, related products.[27]

Genospheres
Researchers at California Pacific Medical Center and Hermes Biosciences, Inc., have developed a nanoparticle-nucleic acid complex for *in vivo* gene delivery. The nanoparticle is a cationic liposome, which can encapsulate DNA under special conditions that render both the lipid and the DNA "molecularly and micellarly soluble *prior* to their combination."[28] The result is a nanoparticle-nucleic acid complex that has the potential for high transfection efficiencies, and that is stable in aqueous solutions.[29]

Organically Modified Silica Nanoparticles
Silica nanoparticles are another alternative for use in non-viral vectors.[30] Researchers at the University of Buffalo "have for the first time delivered genes into the brains of living mice" using organically modified silica nanoparticles "with an efficiency that is similar to, or better than, viral vectors and with no observable toxic effect."[31] Surface-functionalized silica nanoparticles can "bind and protect plasmid DNA from enzymatic digestion [and] transfect cultured cells and express encoded proteins."[32] The organic modification has added benefits: the particles can be "loaded with either hydrophilic or hydrophobic drugs/dyes"; "they can be precipitated in oil-in-water microemulsions, in which corrosive solvents…and complex purification steps…. can be avoided"; the "organic groups can be modified further for attachment of targeting molecules"; and "they can be possibly biodegraded through the biochemical decomposition of the [silicon-carbon] bond."[33] The organically modified silica nanoparticles have been shown to protect the DNA from enzymatic degradation and "release the genetic material inside the cytoplasm, which diffuses to the nucleus…."[34] The vectors have been used to successfully transfect cultured cells, but this technology has not yet moved to clinical trials.[35]

Therapeutic Applications of PLGA Nanoparticles
Researchers have found that nanoparticles made of a certain polymer (PLGA) can deliver DNA to areas in the body previously inaccessible to larger particles.[36] Scientists have also demonstrated that nanoparticles can produce highly efficient *in vivo* gene transfection and sustained gene expression.[37] In addition, the nanoparticles are non-toxic and can be designed to be biocompatible in order to avoid the immunogenicity problem.[38] As noted above, toxicity limits dosage. Because the polymer nanoparticle is non-toxic *in vitro* and *in vivo*, the "dose of nanoparticles could be increased to deliver the required amounts of DNA without the concerns over nanoparticle associated toxicity."[39]

pRNA Nanotechnology
The Guo Group at Purdue has been investigating a nanoparticle/RNA combination for gene transfer to treat cancer.[40] According to Guo, Khaled, et al., "the development of a safe, efficient, specific, and non-pathogenic system for the delivery of therapeutic RNA is highly desirable," because nanoparticles "could move out of blood vessels or kidney during circulation and have a shorter retention time in the body."[41] Guo has used phi29 Motor (packaging) RNA (pRNA) as a delivery mechanism for therapeutic RNA.[42] "The structural and molecular features of…pRNA allow its easy manipulation, making it possible to redesign its parts as gene-targeting and delivery vehicles."[43]

Synthetic Biology
Synthetic biology is usually discussed separately from gene therapy. Yet gene therapy is one potential application of synthetic biology,[44] and synthetic biology is in part nanotechnology.[45] DNA, an essential building block for synthetic biologists, is a nanoscale molecule.[46] That alone is not enough to make synthetic biology a nanotechnology. However, to the extent that synthetic biology research exploits and manipulates nanoscale properties, it can properly be seen as part of nanotech.

Synthetic biology is "the design and construction of new biological parts, devices and systems that do not exist in the natural world."[47] It is also "the redesign of existing biological systems to perform specific tasks."[48] Synthetic biologists may seek to "employ nonnatural molecules to mimic biological behavior and to assemble well-characterized biomolecular components into circuits that perform prescribed functions."[49]

What makes synthetic biology different from other biotechnology endeavors is the manipulation of DNA to construct novel parts and systems to perform specific tasks.[50] From this definition, the applications for gene therapy become apparent.[51] With synthetic biology, a researcher can construct gene delivery vectors and can encode them with specific gene sequences; the vectors could even be self-replicating.[52]

Gene Therapy Oversight as a Model for Nanobiotechnology

The above review shows that nanotechnology is already being used in gene transfer research. This means that the oversight system for human gene therapy

— anchored in the Office of Biotechnology Activities (OBA) at NIH and in the Center for Biologics Evaluation and Research (CBER) at the FDA — is already beginning to grapple with the task of overseeing nanobiotechnology. Indeed, the meeting minutes of OBA's Recombinant DNA Advisory Committee (RAC) reflect this. RAC minutes from September 17-18, 2007, for example, reflect some attention to the increasing relevance of nanotechnology.[53] The committee heard a presentation on "nano-particle mediated drug delivery." Then "RAC members offered several comments about the safety of nanoparticles and about protecting laboratory workers, particularly since these are small enough to pass through high-efficiency particulate air filters, which have a maximal efficiency of around 200 nanometers."[54]

The RAC is reviewing protocols that utilize nanotechnology, although it is difficult to assess the exact numbers as many investigators do not explicitly use the term "nanotechnology" in their protocol or methodology. One protocol listed for committee review on a 2007-08 RAC agenda is identified as using nanotechnology:[55] protocol #0804-914, a Phase 1, open-label, dose-escalation study to "Assess the Safety and Tolerability of the BikDD Nanoparticle in Patients with Advanced Pancreatic Cancer."[56] The minutes reveal attention to toxicity and safety concerns.[57] Minutes from that same meeting reflect concerns about the nano delivery method in a similar protocol (#0804-913, a Phase 1 Study of BikDD Therapy in Advanced Breast Cancer), in that "liposome nanoparticles are known to accumulate at high levels in normal tissues, including lung and heart, in addition to the targeted tumor cells."[58] Review of both protocols resulted in a decision to include comments and concerns in a letter to the investigator and sponsor.[59]

This article thus examines the strengths and weaknesses of the gene therapy oversight system at a crucial moment, as the system faces the new challenge of nanobio oversight. However, the article does more than analyze the capacity of the gene therapy oversight system to cope with nanobio. That oversight system is one of a number of U.S. oversight regimes beginning to face nanobio; the FDA, EPA, U.S. Department of Agriculture (USDA), and Occupational Safety and Health Administration (OSHA) are prominent agencies facing the same challenge as well. Each of these oversight authorities is facing the question of whether their existing oversight approaches are adequate for nanobio or other approaches are needed. Indeed, this is a question facing oversight authorities around the globe.

To provide guidance for the U.S. debate, our project group based at the University of Minnesota received funding from the National Science Foundation (NSF) to analyze U.S. oversight models germane to nanobio oversight. The goal has been to identify strengths and weaknesses, in order to inform the nanobio oversight debate and help shape development of adequate nanobio oversight approaches. The five case studies we have analyzed are oversight of genetically engineered organisms (GEOs) in the food supply, pharmaceuticals, medical devices, chemicals in the workplace, and gene therapy. This article presents the gene therapy oversight case study. Oversight of gene transfer research in human participants is an important model for nanobiotechnology oversight. Of the five case studies we developed, it is the one most fully focused on oversight of human subjects research. Nanobiotechnology itself now spans bench research, human subjects research, product development, and product marketing. However, much of the science, especially in nanomedicine, is entering or in human research trials.

The well-documented history and evolution of gene therapy oversight exemplifies a certain set of approaches to oversight of research. It is a compelling story that shows problems (and strengths) in oversight by two very different agencies at once (at NIH and the FDA), with tensions between public openness and protection of proprietary information, preventing harm and retarding scientific progress, creating standards and adapting to evolving science. The gene therapy oversight story (which is still unfolding) has much to teach those struggling with design of nanobio oversight. And, as indicated above, gene therapy oversight authorities themselves are just beginning to address nanobio directly.

To unpack the gene therapy oversight story and the lessons it offers, we start by providing a brief history of the gene therapy oversight framework, starting with the roots of this system in oversight of recombinant deoxyribonucleic acid (rDNA) research more generally. We then analyze the gene therapy oversight system, using an assessment methodology designed for all five case studies but going beyond that to analyze the literature and history. Finally, we derive the lessons for nanobiotechnology oversight.

History of Gene Therapy Regulation

Gene therapy oversight and regulation has roots in the recombinant DNA (rDNA) controversy that emerged in the early 1970s. Recombinant DNA research involved splicing together DNA from different sources to create a new sequence, which could then be transferred via a virus into another organism through a process called transduction. This process had the potential for high impact: the ability to manipulate and modify genetic material held enormous potential, but there was also

concern that rDNA could also have catastrophic physiological and environmental consequences. Scientists and policy makers grappled with the question of how to move forward while creating adequate safeguards.

In the spring of 1971, Paul Berg at Stanford University proposed an experiment that would combine a tumor virus with a bacteriophage that occurs naturally in *Escherichia coli (E. coli)*.[60] The tumor virus was simian virus 40 (SV40), known to cause tumors in hamsters.[61] SV40 also affected human cells in the lab.[62] *E. coli* occurs naturally in the human digestive track.[63] The danger was that the research would inadvertently create a way for the SV40 tumor virus to cultivate in *E. coli*,[64] creating a cancer risk for humans.[65]

Histories of this era recount that Berg was confronted by Robert Pollack from the Cold Spring Harbor Laboratory on Long Island.[66] Pollack was concerned about the cancer risk Berg's research presented.[67] Pollack stressed that research of such profound magnitude should not be done in secret, leaving the rest of the scientific community, and indeed the rest of society, to clean up any deleterious effects.[68] Berg postponed the research while seeking further counsel from his peers.[69] The result was an indefinite postponement of the rDNA experiment at Stanford, and the first self-imposed moratorium on rDNA research.[70] Contemporaneously, Stanley Cohen had developed his own techniques for recombinant experimentation, but he also recognized the dangers inherent in this research and similarly imposed a moratorium.[71]

Out of this grew a conference on laboratory containment at the Asilomar conference center in California in January 1973 (Asilomar I). The major concern was whether the SV40 virus would cause cancer in humans.[72] Safety precautions were also outlined, but the general conclusion was that the cancer risk was less than previously feared.[73]

Scientists met at a Gordon Conference on Nucleic Acids in June 1973 to discuss recent research findings including in rDNA research.[74] Safety concerns were raised again.[75] The consensus was to draft a letter of concern to the National Academies of Science (NAS) expressing that along with the potential benefits of rDNA research came a potential hazard to "workers and the public."[76] The letter suggested that NAS assemble a committee to address this concern and establish guidelines[77] and was published in *Science*.[78] NAS, through the Assembly of Life Sciences, organized a study committee, and Paul Berg was asked to head the committee, to create mechanisms for reviewing the potential dangers and benefits of rDNA research.[79]

Berg's committee made four recommendations in what came to be known as the "Berg letters": (1) a moratorium should be declared on certain experiments, particularly those that might create antibiotic-resistant strains, and experiments combining tumor viruses with non-tumor viruses and/or bacteriophage; (2) the risks and rewards of linking animal DNA to plasmid or phage DNA should be carefully weighed; (3) the Director of NIH should establish "an advisory committee to evaluate hazards of recombinant DNA, develop procedures to minimize those risks, and devise guidelines for work with [rDNA]" (eventually, this would be the RAC); and (4) domestic and international scientists should convene "to discuss appropriate ways to deal with the potential hazards of [rDNA] molecules."[80] In explaining why the committee urged a moratorium, Berg said, "[W]e feel that the scientific community should be given a chance to regulate itself in its movement in the future.…I think most scientists agree very readily that the hazard is there and would like to see the hazard removed in some way, either by showing that…it's just a potential…or that we change the technology [for this kind of research] in a way that avoids it."[81]

In February 1975, cellular biologists from around the world met for a second conference at Asilomar (Asilomar II) to discuss recombinant DNA research.[82] Of particular concern was whether the moratorium on certain rDNA research should continue.[83] The topic was hotly debated.[84] Some felt that the hazards were too speculative, while others believed that the potential dangers were too great to proceed without safeguards.[85] The conclusion was that rDNA research should proceed, but with safeguards, building containment into experimental design and calibrating containment to match estimated risk.[86] This risk analysis would be difficult at first, but would eventually become easier.[87] The risks were met with robust methods of containment, including biological barriers.[88] Education and training were also stressed in order to maximize the effectiveness of biological barriers.[89]

The Rise of the RAC

Only a few months earlier, in October 1974, NIH had established the Recombinant DNA Molecule Program Advisory Committee (later shortened to Recombinant DNA Advisory Committee or RAC).[90] The first RAC chair was the NIH Deputy Director for Science DeWitt Stetten, Jr., appointed by NIH Director Robert Stone.[91] RAC membership was later broadened by Joseph Califano as Secretary of the Department of Health, Education and Welfare (DHEW) to include ethicists, lawyers, and lay persons, among others.[92] The inclusion of non-scientists at first "sparked [the scientists'] spirited resistance," but after some time, "many of the scientists who originally opposed the

action appreciated some of the benefits of broad public participation."[93]

RAC's first task was to create a set of guidelines consistent with the recommendations that came out of the second Asilomar meeting.[94] In addition, the RAC's role was to advise the NIH Director "on (i) the conditions which the NIH should impose on its grantees and contractors working with recombining DNA molecules, (ii) the level of effort the NIH should make to provide high containment facilities, and (iii) steps NIH should take to stimulate research to reduce the biohazards."[95]

The RAC developed guidelines that were consistent with the Asilomar consensus, publishing them in the *Federal Register* in July 1976.[96] The guidelines included a list of prohibitions on (1) "cloning of [rDNA] derived from...[certain] pathogenic organisms"; (2) "[d]eliberate formation of [rDNA] containing genes for the biosynthesis of toxins"; (3) "[d]eliberate creation from plant pathogens of [rDNA] that are likely to increase virulence"; (4) "[w]idespread or uncontrollable release into the environment of any organism containing a [rDNA] molecule unless [there was]...no reasonable doubt of safety"; (5) "[t]ransfer of drug-resistant traits to organisms...not known to acquire them naturally should be deferred"; (6) "large-scale (e.g., more than 10 liters of culture) experiments."[97]

By 1976, Donald Fredrickson had taken over as Director of NIH.[98] Under his leadership, the RAC published proposed guidelines for rDNA research in the *Federal Register*,[99] with public hearings required before the guidelines could be finalized.[100] The choice of guidelines as opposed to regulations was deliberate.[101] In his memoir, Fredrickson recalled a meeting with the NIH regulations officer, who described the differences between guidelines, regulations, and rule making:

> Guidelines. Simply a statement of rules or procedures that people are expected to follow...does not have the force of law.…NIH has implied authority to issue guidelines without higher level authority.
>
> Regulations. As used in government circles has a precise technical meaning: Refers to substantive rules of general applicability adopted as authorized by law...that have been published in the Federal Register for the guidance of the public.… Usually subject to long delay and iterative process for revision. Note: The Director of NIH does not have authority to sign or publish a regulation. They must be signed by the Assistant Secretary for Health and approved by the Secretary.[102]

The major reason for avoiding regulation was to avoid delaying scientific progress.[103] Guidelines also seemed to allow the scientific community to monitor itself.[104] Nonetheless, researchers receiving federal funding for rDNA research had to follow the guidelines under pain of having their funding stripped.[105]

In 1980, Martin Cline conducted the first gene transfer experiments involving human participants.[106] However, Cline's attempts to get approval from the IRB at UCLA had failed.[107] He conducted his experiments in Israel and Italy,[108] but it was later determined that he misled Israeli and Italian regulators as to the nature of the intervention, and misled human subjects.[109] Cline was censured and stripped of NIH grants.[110] Cline's actions sparked new debate about the use of rDNA in human subjects.

In 1980, the White House commissioned a report on the social and ethical issues raised by genetic engineering in human beings.[111] In 1982, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research released a report on *Splicing Life*.[112] The report noted the need for regulatory oversight and recommended change in the RAC. The report suggested that RAC should be independent from funding agencies such as NIH and called for more involvement by other federal bodies.[113]

In 1982, Representative Albert Gore, Jr. (D-TN) convened congressional hearings on gene therapy.[114] Alexander Capron presented *Splicing Life* to the committee members.[115] Participants agreed that the federal government should establish an oversight body to review social and ethical issues.[116] Many felt that the RAC did not have the "institutional independence to evaluate objectively research promoted by other organs of NIH."[117]

The 1982 hearings yielded two important results. First, the Office of Technology Assessment (OTA) wrote an influential report on "Human Gene Therapy."[118] The report concluded that somatic cell gene therapy was not significantly different from conventional medical techniques, in contrast to germ-line gene therapy. Somatic cell therapy targets ordinary body cells and so is not expected to create heritable changes; in contrast, germ-line gene therapy affects cells in the gonads, creating heritable changes.[119] The report also concluded that existed oversight methods were adequate, though it noted the conflict of interest that the RAC might have in reviewing NIH-funded research.[120]

Second, in 1984 RAC formed a Working Group to focus on human gene therapy (which later became the Human Gene Therapy Subcommittee (HGTS)), largely in response to the *Splicing Life* report.[121] The

group was chaired by LeRoy Walters.[122] In 1986 the Working Group published "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols," to guide gene therapy protocol preparation and review.[123] This augmented the general review process for human subjects research, which required approval from the IRB at the researcher's institution.[124] Under the "Points to Consider," a proposal first required approval by the local Institutional Biosafety Committee (IBC) and IRB (though the IBC and IRB could make their approval contingent upon RAC deliberation). Then the proposal went to the RAC for consideration, though it could be considered concurrently by other federal agencies, most probably the FDA. As part of RAC consideration, a summary of the proposal would be published in the *Federal Register* for public comment. The Working Group and then the RAC would consider the proposal and forward a recommendation to the Director of NIH. The NIH Director could approve proposals only if he or she found they presented "no significant risk to health or the environment," and the Director's decision would be published in the *Federal Register*.[125]

The Rise of FDA Review

While NIH was establishing RAC and Working Group review, the FDA was establishing its own review process. In 1984 the FDA began to assert jurisdiction over gene therapy regulation by announcing that it would regulate rDNA-derived products under both the Public Health Services Act (PHSA) and the Food, Drug, and Cosmetic Act (FDCA) § 201(p)(1).[126] The FDA decided to classify gene therapy products as "biologics" in the mid-1980s,[127] lodging gene therapy oversight in the Office of Biologics Research and Review, in the Center for Drugs and Biologics (CBER).[128] The FDA classifies products as biologics, drugs, or devices; biologics are regulated under the PHSA,[129] while drugs[130] and devices[131] are regulated under the FDCA. The FDA published its own "Points to Consider" document in 1991 for researchers interested in pursuing gene therapy research and clinical investigations.[132]

In 1993 the FDA made clear that it intended to regulate gene therapy solely through the existing regulatory framework.[133] The agency published a document in the *Federal Register* outlining which statutes and regulations applied to gene therapy products.[134] The document bifurcated gene therapy products into two groups — those using viral delivery vectors and those using non-viral vectors.[135] The FDA clarified that the former would be regulated as "biologics," but the latter as "drugs."[136] Nonetheless, gene therapy oversight remained housed primarily in CBER.[137]

Approving the First Clinical Trial

Even as the FDA began to assert its role, it continued to share responsibility for gene therapy regulation with the NIH. In 1988, three NIH researchers submitted the first protocols for gene therapy clinical trials.[138] French Anderson of the National Heart, Lung, and Blood Institute (NHLBI), along with Michael Blaese and Steven Rosenberg of the National Cancer Institute (NCI), had designed a method of tracing tumor infiltrating lymphocytes (TIL).[139] This research was not intended to treat disease, but rather to introduce "marker" genes that scientists could then use to follow the cancer-fighting TIL cells.[140] However, the research required multiple approvals — from the IRB at NHLBI, the IRB at NCI, the Institutional Biohazard Committee at NIH, a hospital safety committee, the HGTS of the RAC, the full RAC and NIH Director, and the FDA.[141] By now the complexity of the oversight system was pronounced.[142]

The HGTS was the only one to object, finding the data presented insufficient to show that the TIL procedure was safe and requesting additional information. The research team, however, declined to produce more data, concerned that it would compromise their chances of publishing. In response, HGTS deferred approval until further data were available.[143]

Not wanting to wait, the research team took their case to the full RAC. In front of the RAC, Anderson contrasted the risk posed to already-dying research participants with the potential benefit to hundreds of thousands of cancer patients. This strategy worked, and the RAC voted to approve. NIH Director James Wyngaarden had the HGTS reevaluate the TIL protocol. The HGTS on reconsideration recommended RAC approval.[144]

Because the TIL protocol involved a product derived from gene therapy research, Anderson and his colleagues needed FDA approval as well. The FDA considered rDNA products to be "investigational new drugs" (IND) subject to premarket approval.[145] Anderson's team had submitted an IND application the previous October, and directly following RAC approval the FDA approved as well. In May 1989, the research team oversaw the first infusion of genetically modified TILs into a patient dying of melanoma.[146] This marked the first gene transfer clinical trial.[147] Less than a year later, Anderson, Blaese, and Kenneth Culver obtained RAC and FDA approval to conduct gene transfer research on a 4-year old girl suffering from severe combined immunodeficiency disorder (SCID).[148]

An Altered Role for the RAC: 1996-Present

In the early 1990s, gene transfer research enjoyed popular support.[149] The number of protocols submit-

ted to the RAC increased rapidly. Eventually, however, the RAC was reviewing protocols identical or similar to those it had already approved.[150] During a 1991 meeting of the RAC, Anderson warned that the complex federal oversight system would push researchers to private sources of funding to avoid all except FDA oversight.[151] Under pressure to streamline the RAC, the NIH consolidated procedural hurdles in 1992 by merging the HGTS back into the RAC.[152] The RAC continued, however, to review *all* proposed protocols.[153] The National AIDS Task Force recommended that NIH and FDA review processes be combined.[154] In response, the NIH and FDA issued a *Federal Register* notice outlining a more collaborative working relationship.[155] This agreement progressively transferred "case-by-case review of protocols to the FDA, with the FDA and [RAC] jointly deciding on the need for public review."[156] It further provided that the FDA and RAC had "agreed to hold public prospective discussions on major ethical issues such as *in utero* and germline gene therapy protocols."[157]

Under further pressure to remove unnecessary research impediments,[158] then-NIH Director Harold Varmus proposed in July 1996 to discontinue the RAC.[159] In doing so, he hoped to eliminate overlapping roles between NIH and FDA.[160] The NIH and FDA themselves were in substantial agreement that a coordinated framework for gene therapy oversight was needed.[161] However, Director Varmus's proposal encountered significant public resistance, demonstrating the positive reputation the RAC had built.[162] In response, the Director revised his proposal, retaining the RAC but reducing the scope of its authority. This new proposal cut the RAC's membership to 15 members[163] and withdrew its power to approve individual gene transfer protocols.[164] In its revised role, the RAC would function as an advisory panel, rather than an approval body. It would discuss novel gene transfer protocols, convene gene therapy policy conferences, and maintain public access to information about human gene transfer trials.[165] In 1997 these recommendations took effect.[166] The FDA now had sole responsibility for approving both gene therapy protocols and gene therapy products for commercial sale.[167] While these changes effectively stripped the RAC of its approval authority for individual trials, the new guidelines continued to require researchers to submit proposed protocols to both the NIH and the FDA.[168] The NIH also retained guidelines requiring researchers to report unexpected Serious Adverse Events (SAEs) during clinical trials directly to the NIH.[169]

In 1999, 18-year-old Jesse Gelsinger died from the effects of a gene transfer protocol designed to address ornithine transcarbamylase (OTC) deficiency.[170] The gene transfer research was conducted at the University of Pennsylvania.[171] While not the first death during a gene therapy clinical trial, Gelsinger was the first whose death was directly attributed to the adenoviral vector.[172]

The investigation that followed revealed several problems with the oversight framework for gene transfer research. First, the FDA had not informed the RAC that it had authorized a change in the mode of administering the adenoviral vector in the OTC protocol in which Gelsinger was enrolled.[173] Second, the Principal Investigator on the clinical trial had failed to disclose that he founded the company that owned the rights to any treatments developed from the clinical trial;[174] this conflict of interest, if disclosed, might have influenced Gelsinger's decision to participate. Third, the transfer of approval authority from the RAC to the FDA had resulted in an informed consent process less amenable to public review.[175] Finally, it emerged that multiple SAEs leading to death in other trials had not been reported to NIH,[176] while all had been reported to the FDA.[177] Because the FDA kept reports of SAEs confidential, researchers were more likely to comply with the FDA's reporting requirements.[178] Private organizations had requested that SAE reports be kept from the public for proprietary reasons,[179] and the FDA (unlike NIH) provided protection of proprietary information.[180]

In response to these findings, the RAC was given a slightly larger, though still advisory, role. Under an October 2000 amendment to the NIH guidelines, NIH-funded researchers had to submit proposed gene transfer protocols to the RAC for evaluation of whether public review was needed *before* Institutional Biosafety Committee (IBC) approval could be granted.[181] While the RAC's post-1997 function had become purely advisory,[182] NIH guidelines had required plenary, public review of "protocols that presented unresolved safety or ethical issues."[183] To determine which proposed protocols warranted public review, RAC committee members voted.[184] If a protocol was selected for public review, the review usually followed review by the local IRB.[185] The 2000 amendment had the effect of positioning RAC review before IBC and IRB action.[186] This timing change allowed both the IBC and the IRB to make better use of the RAC's evaluation of the proposed protocol.[187]

In addition, post-Gelsinger both the NIH and the FDA revised SAE reporting requirements to increase inter-agency consistency. Prior to the Gelsinger tragedy, the NIH guidelines required immediate reporting of all adverse events,[188] "regardless of whether the SAE was expected or unexpected and whether the SAE was related or unrelated to the study therapy."[189] In Decem-

ber 2001, the NIH "harmonization action" became effective.[190] This action made the NIH reporting requirements for SAEs consistent with FDA reporting requirements. Under the new guidelines, a SAE had to be reported immediately to both the FDA and NIH if the adverse event was "serious *and* unexpected *and* related to the study therapy."[191] Investigators had to report such an SAE within 7 days if the unexpected SAE was fatal or life-threatening and within 15 days if it was not fatal or life-threatening.[192] These changes narrowed the definition of SAEs requiring immediate reporting to the most serious. By narrowing reporting requirements, the agencies hoped to focus more carefully on those SAEs that were reported.[193]

The current regulatory framework remains a relatively complex mix of federal and local oversight. Federal authorities involved include not only the RAC and OBA at NIH, as well as CBER at the FDA, but also the Office for Human Research Protections (OHRP) at DHHS; local authorities include the IRB and IBC at the researcher's institution.

Both the NIH and FDA also instituted changes to remedy challenges posed by FDA's proprietary protection and NIH's publication of SAEs. Disclosure of SAEs posed two risks: that confidential proprietary information would be disclosed, and that an uninformed public would overreact to SAE data.[194] Keeping the information private at FDA, however, had inhibited oversight and inter-agency cooperation. The NIH responded to these challenges by creating the Genetic Modification Clinical Research Information System (GeMCRIS). This online database allowed controlled release of SAE information, depending on the user's identity.[195] The FDA, for its part, proposed to begin disclosing SAEs that it had previously kept confidential.[196] Finally, the FDA and NIH also agreed to share information on SAE reports they received.[197]

Post-Gelsinger, NIH also began to address the conflicts of interest that could arise in commercially supported gene therapy research.[198] As one writer has noted, "Intense commercial interest in gene therapy may create conflicts between business decisions and medical decisions."[199] That writer outlined conflict-of-interest concerns in the Gelsinger case:

> Dr. James Wilson, the head of the Institute for Gene Therapy at the University of Pennsylvania, also owns a private company called Genovo, Inc.... Genovo has the rights to any discoveries made by Wilson at his University of Pennsylvania lab. Through this arrangement, Genovo has access to Wilson's discoveries.... Genovo also has a financial stake in the adenovirus variation Wilson developed and tested on Jesse in the human gene therapy trial, which would have been very marketable if it had been successful.[200]

Current Gene Therapy Oversight Framework

The current regulatory framework remains a relatively complex mix of federal and local oversight.[201] Federal authorities involved include not only the RAC and OBA at NIH, as well as CBER at the FDA, but also the Office for Human Research Protections (OHRP) at DHHS; local authorities include the IRB and IBC at the researcher's institution.[202]

Gene therapy products require premarket approval from the FDA before they can be marketed and sold.[203] The FDA will grant approval only based on a demonstration that the product "is safe, pure, and potent."[204] Furthermore, a product's effectiveness in achieving its intended result must be demonstrated as part of the showing of potency.[205]

Gene therapy trials on human participants require that the researcher/manufacturer submit an Investigational New Drug Application (IND) to the FDA. In the IND, the researcher/manufacturer must detail the proposed clinical trial, providing information on anticipated risks to study participants and supporting scientific data.[206] The IND process requires obtaining local IRB approval as well. As part of FDA review of the IND application, the "FDA may ask the study sponsor to do more laboratory tests and include more safeguards to ensure the safety of patients, such as giving patients smaller doses."[207] The FDA has the authority to require study changes or cessation, if problems arise.[208] FDA authorities oversee not only study design and execution, but also manufacturer compliance with FDA rules for producing gene therapy products.[209] The FDA maintains a Gene Therapy Patient Tracking System (GTPTS) to offer enhanced oversight of gene therapy trials and products.[210]

Researchers must also submit proposed clinical trials to the RAC for NIH-funded protocols.[211] Information on the proposed trial is sent to RAC members,

who determine whether the proposed research raises "important scientific, safety, medical, ethical, or social issues that warrant in-depth discussion at the RAC's quarterly public meetings."[212] In contrast to the FDA oversight system, public openness is a key feature of the RAC review process. The goal of RAC review is to advise the NIH Director and OBA, both on proposed research protocols and on changes needed in the relevant guidelines. This advisory role is distinct from FDA's role in providing needed approval.[213] In addition to RAC review (as well as public review, if selected by the RAC) and FDA review, the protocol must be approved at the local level by the IRB and IBC at the researcher's institution before the research can proceed.[214] While the FDA has approved many clinical trials, it has not yet approved any gene therapy products for commercial sale.[215]

Gene therapy researchers have reported a number of additional SAEs since the Gelsinger case. In September 2002, a French patient developed leukemia-like symptoms after receiving gene therapy.[216] The French researcher in charge, Alain Fischer of Hôpital Necker-Enfants Malades,[217] reported the first leukemia case to the French authorities.[218] With the Gelsinger experience still fresh, the FDA immediately put on hold U.S. gene therapy research on X-linked severe combined immunodeficiency (XSCID).[219] When a second patient developed the same symptoms in January 2003, the FDA put a hold on all trials involving hematopoietic stem/progenitor cells.[220] Fischer reported on these SAEs to the RAC via teleconference during the RAC's February 2003 meeting.[221]

In July 2007, Jolee Mohr died in a Chicago hospital, about three weeks after receiving an injection of genetically engineered viruses designed to treat rheumatoid arthritis in her knee.[222] After several weeks of investigation, the cause of her death remained unknown. In November 2007, the FDA gave the research company, Targeted Genetics, permission to resume clinical trials of the gene therapy.[223] A preliminary review of the protocol revealed that the gene transfer was an unlikely cause of the fatality.[224] At a December 2007 meeting, the RAC concurred, finding that an immune response to the vector for the gene therapy treatment was not the cause of death.[225] The RAC also concluded that the adeno-associated vector used to deliver the DNA was safe for participants in the Targeted Genetics trial.[226]

Researchers continue to conduct gene transfer research. As of 2005, there had been more than "1,000 different gene-therapy clinical trials for the treatment of many different diseases."[227] In 2007, Charles Lu at M.D. Anderson Cancer Center in Houston, Texas began the first human clinical trials of non-viral nanogene therapy.[228]

Assessing Gene Therapy Oversight

This section reports on public attitudes toward gene therapy, an expert elicitation process that we conducted as part of the NSF-funded project in which we participated involving assessment of five oversight systems, and finally a synthesis of these sources with assessments suggested by the secondary literature and the history recounted above.

Public Opinion of Gene Therapy and Implications for Oversight

The now-expired Office of Technology Assessment (OTA) published in 1987 what remains a signal study of public attitudes toward genetic engineering and gene therapy.[229] The OTA conducted a nationwide survey with a focus on genetic engineering and biotechnology.[230] The data continue to be relevant to assessing public attitudes toward gene therapy and its oversight.

The OTA found that "[a] majority of those who feel human gene manipulation in general is morally wrong nonetheless says it would approve its use in specific therapeutic applications."[231] Approval numbers for gene therapy were impressive: 84% approved gene therapy to prevent children from inheriting a typically fatal genetic disease; 83% to cure such a disease; 77% to prevent children from inheriting a nonfatal birth defect; and 77% to lower the risk of developing a fatal disease later in life.[232] Seventy-eight percent said they would be willing to undergo gene therapy if they discovered they were likely to develop a serious genetic disease later in life, and 86% said they would be willing to have gene therapy administered to their children if they had a fatal genetic disease.[233] These numbers may well have been inflated by description of what was (and still is) gene transfer research, rather than accepted therapy, as if it was the latter. This is a persistent problem in interpreting public surveys on the topic.

Since the OTA survey, further public opinion studies have yielded similar results. A 1992 March of Dimes survey found public opinion showed overwhelming approval (87%) for "scientists changing the makeup of human cells to cure a usually fatal disease" and even (78%) to "reduce the risk of a usually fatal disease."[234] A 1993 *Time*/CNN survey found that 79% approved "of the use of genetic engineering to cure a disease."[235] A 1996 study by the National Center for Genome Resources (NCGR) showed that 86% of respondents approved of "changing the makeup of human cells to prevent/stop children from inheriting a usually fatal

disease"; 85% to "cure a usually fatally genetic disease"; 84% to "reduce the risk of a usually fatal disease"; and 72% to "prevent/stop children from inheriting a usually nonfatal disease."[236]

Polls thus show that safe, effective gene therapy to correct genetic diseases receives high public approval. This opinion has been echoed in Europe. In a 1990 Gallup poll surveying the United Kingdom, France, Italy, and Germany, when respondents were asked about the most important benefits of biotechnology, more than half considered cures for serious diseases to be the most important benefit.[237]

While a majority of Americans approve of therapeutic applications of gene therapy, they see risk involved in science and technology generally. The OTA survey reported that 22% felt advances in science and technology would cause "a lot" of risk to them and their families; 49% believed these developments would pose "some" risk; only 20% saw "little" risk; and a mere 7% saw "no" risk during the next 20 years.[238] Seventy-three percent agreed there was need for regulation to limit the potential danger of genetically altered cells.[239] The OTA concluded:

> Despite the basically positive orientation of the public toward scientific growth and technological progress, there is evidence of growing public support for increased control over technological development. Although a plurality still favors maintaining the current degree of regulatory control over science and technology, the proportion that says it favors increased control has risen from 31 to 43 percent over the past decade. There is a consensus in favor of technological growth, but control over perceived risks is increasingly important to the public.[240]

In keeping with this, a 2002 survey by the Genetics and Public Policy Center found that 71% of Americans polled felt that "government should regulate the quality and safety of genetic engineering."[241]

The public opinion data suggest that Americans have shown optimism about the promise of gene therapy, but also a sense that scientific advances would pose risk. This suggests the need for oversight to assess and control risk, while assuring the safety and effectiveness of gene therapies developed. Debate over proper oversight for gene transfer research has focused to a great extent on safety, as initial ethical concerns sparked by rDNA containment have faded. Signal gene therapy deaths and adverse events have stoked public and professional concern over safety.[242] However, RAC, the bioethics community, scientists, and research participants have recognized a range of issues suggesting need for gene therapy oversight.

Debate over proper oversight for gene transfer research has focused to a great extent on safety, as initial ethical concerns sparked by rDNA containment have faded. Signal gene therapy deaths and adverse events have stoked public and professional concern over safety. However, RAC, the bioethics community, scientists, and research participants have recognized a range of issues suggesting need for gene therapy oversight.

Literature on Gene Therapy Oversight

Human gene transfer research has been a focus of intensive review and oversight from the field's start. In part, the intensity of oversight may grow out of prior concerns over rDNA research and averting harm (described above), and ensuing scientific self-regulation followed by federal and local regulation and oversight. However, literature focusing on human gene therapy, exemplified by the *Splicing Life* report, fortified the commitment to proceed carefully, avoid harm to research participants, and consider the especially problematic issues surrounding germ-line gene therapy and use of gene therapy for enhancement.

The literature on gene therapy oversight has waxed and waned with events. Spikes in the volume of this literature correspond with the initial establishment of the system, NIH reorganization of the RAC in the mid-1990s, and subsequent concern with the revelation of Gelsinger's death and other SAEs, leading to reinvigoration of the RAC.[243]

The 1982 *Splicing Life* report addressed oversight directly. Noting that the RAC had thus far taken the lead on rDNA research, the President's Commission

called for expansion of RAC's role to address use of genetic engineering in human beings. The commission urged that engagement with other federal bodies grow, and suggested moving RAC outside of DHEW (now DHHS) and assuring mixed government and non-government membership would help. The commission discussed options such as creating a Genetic Engineering Commission or using the successor body to the President's Commission.[244] While neither of these options was ultimately used, RAC's role was indeed enlarged to lead analysis of human gene transfer research. Walters and Palmer describe how the analysis in *Splicing Life* led to RAC's creation of the Working Group on Human Gene Therapy, which Walters chaired.[245] The commission's emphasis on the need for an oversight body to educate scientists on ethical and societal concerns, catalyze federal attention to the issues, lead public thinking, operate with scientific sophistication, and address genetic engineering issues comprehensively bore fruit. Indeed, Walters and Palmer note that "[n]umerous countries have established RAC-like committees to provide national review for gene therapy protocols....includ[ing] the United Kingdom, France, Canada, the Netherlands, Italy, and Japan."[246]

Walters and Palmer contrast the RAC model with two others: a presidential commission and direct congressional action.[247] They note that in 1983, then-Representative Gore introduced a bill to establish a President's Commission on the Human Applications of Genetic Engineering. This new law, if enacted by Congress, would have moved oversight outside of NIH and DHEW/DHHS to a commission appointed by the president. Yet the ultimate resolution — leaving oversight in the hands of the RAC, with complementary oversight at the FDA — allowed Walters and Palmer to note in 1997 that since 1983, "there have been no major initiatives by the United States Congress to regulate human gene therapy."[248]

King has analyzed RAC's oversight history and function, concluding that the oversight of human gene transfer research is a powerful oversight model.[249] Since all human subjects research supported by federal funds or conducted by institutions that provide a general assurance that their research will be conducted following federal rules undergoes IRB review, and all medical products offered for sale in the United States require FDA approval, King anchors on the question of when the added layer of scrutiny provided by the RAC is warranted. She suggests that in reviewing proposed research protocols, RAC acts like a central, federal IRB combined with a scientific study section that NIH would use to review the merits of proposed research. In RAC's other function, public education and policy making, the RAC has the capacity to address and advance discussion of vexing social and ethical issues. King argues that this kind of oversight is helpful when the science is complex, uncertainty is high, and difficult ethical issues cut across individual protocols. She concludes that "the model should be extended when... field-wide guidance is needed and useful; cross-study analysis of research data...is both possible and desirable; and public access and education are desired."[250]

One of the authors (Wolf) has analyzed the RAC model as well, in arguing that use of a RAC-style body (which could be RAC itself) to analyze the issues raised by cloning would be superior to a congressional ban.[251] Wolf suggested that it was a mistake to analyze the RAC as merely an advisory body, because the RAC has been effective in forestalling germ-line gene therapy, through the moratorium imposed by in its Points to Consider document. She argued that RAC oversight demonstrated the capacity to set limits but also the flexibility to evolve with the science, responding to complex scientific and ethical challenges in a more nuanced way than Congress itself could. Indeed, surrendering cloning to Congress risked making cloning a "political football"; a RAC approach offered more insulation from the winds of politics to craft solutions to complex scientific challenges.

One frequently articulated concern with RAC oversight is its limited application to privately funded research.[252] Human gene transfer research that is federally funded or conducted at institutions that receive federal research funding must go through RAC review.[253] However, this leaves a domain of privately funded research that need not go to the RAC (though it must still undergo FDA review if the sponsors seek to develop a product to be marketed in the United States).[254] While some privately funded research is voluntarily submitted to the RAC for review, this nonetheless leaves some human gene transfer research that is not subjected to RAC oversight.[255]

The relationship between RAC and FDA oversight has provoked commentary, including complaints that this dual review system is overly burdensome. Walters and Palmer, however, stress the complementarity of the two oversight regimes: RAC review is public and involves a substantial proportion of non-government members, while FDA oversight is conducted confidentially and in-house.[256] Former-FDA Commissioner David Kessler and colleagues addressed the relationship in a 1993 article, describing complementary functions: the RAC "ensures broad public discussion...particularly with regard to social and ethical concerns," while "[t]he FDA focuses on the development of safe and effective biologic products, from their first use in humans through their commercial distribution."[257]

Kessler et al. describe a detailed FDA oversight process, requiring not only an IND application, but also a product-license application and an establishment-license application and ongoing interaction between sponsors of gene therapy research and CBER. This dual oversight system is actually a triple oversight system, as both NIH and the FDA additionally rely on local oversight by the researcher's institutional IRB and IBC.[258]

In some ways the dual oversight system for gene therapy can be seen as a fascinating experiment in alternative approaches to oversight. The RAC system relies on an oversight committee with strong scientific and ethics expertise drawn from outside government. The committee's review is open and public. This is an oversight approach analyzed by Sheila Jasanoff in *The Fifth Branch* as well as others.[259] In contrast, the FDA oversight approach to gene therapy relies heavily on assessment by governmental entities in dialogue with private companies and protecting proprietary information. The contrast between these two approaches is so fundamental, that they seem grounded in different regulatory theories. An analysis of regulatory theories such as Steven Croley's, for instance, might most closely associate RAC's public deliberation with a civic republican approach to regulation, while seeing the FDA's engagement with gene transfer research sponsors behind closed doors as a domain of public choice theory.[260] By combining the two very different approaches used by the RAC at NIH and the FDA, gene therapy oversight invites comparison between the two as well as exploration of whether combining the two approaches works and is worthwhile. Though Walters and Gage laud the complementarity of the two oversight systems, the Gelsinger problem and subsequent revelation that the FDA knew of SAEs undisclosed to the RAC show problems in harmonizing and integrating the two systems and the perils of protecting proprietary information while attempting complex, coordinated oversight.

Scientific developments continue to raise anew the question of whether RAC and FDA review as presently constituted are the best oversight option. The emergence of synthetic biology, for example, has raised the oversight question again. Synthetic biology is developing the capacity to create organisms with significantly altered genomes or synthetic genomes, raising a number of concerns including biosecurity. An influential 2007 report addressed governance options, calling for an oversight body similar to the RAC, noting that this could be the RAC itself. [261] The authors argued, however, that the oversight body should report to an official with "security as well as scientific responsibilities," which could be "the NIH Director or a senior official with science and security responsibilities in another Executive Branch Agency."[262] The report also calls for more enforcement of biosafety guidelines, suggesting that this might require evolution in RAC functions or creation of a new body needed for this enforcement function.

Nanobiotechnology is also raising the oversight question, including in human gene transfer research, as noted above. Kessler et al. could have been writing about nanobio when they said in 1993:

> As these novel therapeutic applications are explored and knowledge about risks and benefits accumulates, the FDA's regulatory approach may well be modified. Nonetheless, early clarification of the agency's plan to apply its existing regulatory framework…is more prudent than waiting until the field has matured. This early discussion will facilitate product development by academic and commercial sponsors in line with FDA requirements and the demands of public health. The historical precedents for evaluating emerging forms of biologic technology are clearly established.[263]

This passage is prescient in anticipating the FDA's approach to nanobio so far — apply existing oversight approaches. Whether that will suffice is a matter of debate. In 2007, the Science and Technology Subcommittee of the FDA Science Board voiced serious doubts about the FDA's current capacity to analyze and regulate new and emerging science, including new genomics and nanotechnology. [264] Indeed, they found that "development of medical products based on 'new science' cannot be adequately regulated by the FDA" and they recommended creation of a new cross-agency, cross-disciplinary entity to address "new sciences."[265]

Expert Assessment of Gene Therapy Oversight

As part of our NSF-funded project, we joined with colleagues to design an assessment tool to allow experts to convey their assessment of oversight approaches in the case of gene therapy and four other oversight case studies. The survey that the project investigators and research assistants devised is described in detail elsewhere in this symposium and in previously published work;[266] the version of that survey used for this gene therapy oversight case study is available at <http://lifesci.consortium.umn.edu/publications/research_pubs>.

In order to devise the surveys used in our case studies, we employed a process that combined expert elicitation with literature review and devised a roster of 28 criteria to be applied to oversight systems in each of our

Figure 1
Project Criteria Labels and Descriptions

Label	Criteria Description
D1	Impetus
D2	Clarity of technological subject matter
D3	Legal grounding
D4	Public input
D5	Transparency
D6	Financial resources
D7	Empirical basis
A8	Legal grounding
A9	Data requirements & stringency
A10	Post-market & ongoing monitoring
A11	Treatment of uncertainty
A12	Empirical basis
A13	Compliance & enforcement
A14	Incentives for compliance
A15	Treatment of intellectual property
A16	Institutional structure
A17	Flexibility
A18	Capacity
A19	Public input
A20	Transparency
A21	Attention to conflict of interest
A22	Informed consent
E23	Extent of change
O24	Public confidence
O25	Research & innovation
O26	Health & safety
O27	Distributional health impacts
O28	Environmental impacts

case studies. (See Figure 1.) As noted in the comparative paper in this symposium, "Experts were identified based on several factors including their contributions to the scientific literature, membership on advisory boards [including the RAC] and/or editorial committees of key journals, and status within their respective communities."[267] The criteria fell into 4 categories: 7 criteria pertaining to development of the oversight system, 15 criteria describing attributes of the system once it was developed, one criterion describing the extent of change in the oversight system over time, and 5 criteria assessing outcomes of the oversight system. We then developed a survey instrument that asked expert respondents to rate the oversight system on a 1-100 scale for each criterion, where 1-20 meant improbable, probably not, unlikely, near impossibility; 21-40 meant less than an even chance; 41-60 meant even chance; 61-80 meant probable, likely, I believe; and 81-100 meant near certainty, virtually certain, highly likely (though we gave respondents the option of just using the numerical ranges and ignoring these qualitative definitions of what each number range meant).

In seeking feedback from experts on a preliminary draft of the gene therapy oversight survey, we asked them to rate NIH/RAC oversight separately from FDA oversight and the survey was modified accordingly. We then emailed the survey to potential respondents. We ultimately received 5 completed and anonymous surveys. The responding experts were classified as 2 from industry and 3 from academia, though several of our experts also have past or current government experience as well, serving on the RAC. Because our response rate was low (19%), the results we report should be considered preliminary. In effect, we piloted an assessment strategy that could be used more extensively to evaluate human gene transfer research oversight. We use the preliminary data reported here only to suggest ways to analyze this oversight experience.

As noted in the comparative study, "each case study research group calculated the mean expert rating for each criterion. These mean ratings were then sorted into three ranges (...[up through] 39, 40-60, and 61-100), which are depicted in Figure [2] by an unshaded circle, a half-shaded circle, or a full shaded circle, respectively. We also determined the level of agreement among expert ratings on each criterion; we then classified the level as low (L), neutral (N), or high (H)." This was done by qualitative, visual inspection of histogram representations of expert responses for each of the 28 criteria. The results for the gene therapy study are depicted in Figure 2.

This figure shows that for the NIH/RAC oversight system, features rated highly with high agreement were: in initial development of the system — clarity of technological subject matter (D2) and the empirical basis of the oversight system (D7); as attributes of the operating system — data requirements and stringency (A9), post-market and ongoing monitoring (A10), empirical basis (A12), incentives for compliance with system requirements (A14), treatment of intellectual property (A15), attention to conflict of interest (A21), and informed consent (A22); and no criteria relating to the extent of change or system outcomes. For the FDA oversight system, features rated highly with high agreement were: no features in development of the system; as attributes of the operating system — data

Figure 2

Quantitative Assessment of the Gene Therapy Oversight Systems' Strengths Based on Mean Ranges

The strengths of each of the 2 oversight systems (NIH and FDA) on various criteria are assessed by identifying the range within which the mean score by experts for each criterion falls and the level of expert agreement in rating the criterion. The ranges are presented by circles. A full-shaded circle ● indicates means from 61 to 100. A half-shaded circle ⭘ indicates means from 40 to 60. There were no means from 0 to 39. Levels of agreement among experts are indicated with parenthesized letters (L), (N), (H), indicating low, neutral, or high level of agreement among experts respectively.

Criteria	Gene Therapy			
	Mean NIH	Range NIH (level)	Mean FDA	Range FDA (level)
Development				
D1. Impetus	68	●(L)	56	⭘(L)
D2. Clarity of technological subject matter	80	●(H)	63	●(L)
D3. Legal grounding	54	⭘(M)	74	●(M)
D4. Public input	69	●(M)	50	⭘(M)
D5. Transparency	61	●(M)	50	⭘(L)
D6. Financial resources	65	●(L)	60	⭘(L)
D7. Empirical basis	78	●(H)	71	●(M)
Attributes				
A8. Legal grounding	58	⭘(M)	65	●(L)
A9. Data requirements & stringency	86	●(H)	90	●(H)
A10. Post-market & ongoing monitoring	82	●(H)	91	●(H)
A11. Treatment of uncertainty	72	●(L)	68	●(L)
A12. Empirical basis	88	●(H)	90	●(H)
A13. Compliance & enforcement	63	●(L)	80	●(M)
A14. Incentives for compliance	74	●(H)	78	●(H)
A15. Treatment of intellectual property	80	●(H)	55	⭘(L)
A16. Institutional structure	75	●(M)	58	⭘(L)
A17. Flexibility	60	⭘(M)	63	●(L)
A18. Capacity	73	●(M)	53	⭘(L)
A19. Public input	78	●(M)	58	⭘(L)
A20. Transparency	65	●(L)	55	⭘(M)
A21. Attention to conflict of interest	80	●(H)	65	●(M)
A22. Informed consent	81	●(H)	73	●(M)
Extent of change				
E23. Extent of change	74	●(M)	58	⭘(L)
Outcomes				
O24. Public confidence	61	●(L)	52	⭘(M)
O25. Research	48	⭘(M)	51	⭘(M)
O26. Health and safety	84	●(M)	83	●(M)
O27. Distributional health impacts	66	●(L)	68	●(M)
O28. Environmental impact	73	●(M)	75	●(M)

requirements and stringency (A9), post-market and ongoing monitoring (A10), empirical basis (A12), and incentives for compliance with system requirements (A14); and no criteria relating to the extent of change or system outcomes. Thus, the NIH/RAC system received more high ratings with high agreement than did the FDA system, but neither received high ratings with high agreement on system outcomes (though, as evident from Figure 3 of the comparative paper in this symposium, the FDA's drug oversight system was the only case study of our 5 that did receive such outcomes ratings).

Some of these ratings appear to be at odds with the history of gene therapy oversight and invite interpretation. Expert ratings of the NIH/RAC system as high on post-market and ongoing monitoring seem at odds with the reality that no gene therapy products are yet approved for marketing. This rating is more understandable if it more broadly captures ongoing NIH/RAC attention to issues raised by trials post-review. Similarly, rating the NIH/RAC system high on attention to conflict of interest seems in tension with failure to address the conflicts of interest in the Gelsinger case when reviewing the protocol initially. Indeed, the literature reflects concern over RAC capacity to address conflicts of interest, including the potential conflict that the RAC faces when reviewing protocols to be conducted at NIH by federal researchers themselves. The high rating on this criterion may reflect, however, post-Gelsinger increase in attention to and analysis of conflicts of interest.

What we can conclude is that the NIH/RAC and FDA oversight systems have different characteristics and merit individual assessment. Yet ultimately, gene therapy protocols face a combined oversight system (though, as noted above, some privately sponsored human gene transfer research is not required to go through NIH/RAC review). Our experts agreed on only 4 criteria as strengths in the operation of both oversight systems: data requirements and stringency (A9), post-market and ongoing monitoring (A10), empirical basis (A12), and incentives for compliance with system requirements (A14). The emphasis on data requirements, creating an empirical basis for oversight and means of monitoring, with incentives for failure to supply information (non-approval and, in the case of NIH, potential failure to receive research funds), suggests that the single most important aspect of this system is its information-forcing character. This is very much in keeping with regulatory theory that sees government requirements to disclose information as a key regulatory tool, especially as computer technology enhances the capacity to process and compare large volumes of information.[268]

Figure 3

Qualitative Assessment of the Oversight System's Strengths Based on the Results of Expert Elicitation and Literature Review

The strengths of the combined gene therapy oversight system on various criteria were assessed by comparing the results of quantitative assessment of strengths (based on mean rating scores by experts and level of expert agreement in rating) with the literature review. The results are summarized using black, white, and half black/ half white squares. A black square ■ indicates that the system was strong on that criterion based on qualitative assessment. A white square □ indicates that the system was weak. A half black/ half white square ◘ indicates that the system was neither strong nor weak.

Criteria	Gene Therapy
Development	
D1. Impetus	◘
D2. Clarity of technological subject matter	■
D3. Legal grounding	◘
D4. Public input	◘
D5. Transparency	□
D6. Financial resources	□
D7. Empirical basis	■
Attributes	
A8. Legal grounding	◘
A9. Data requirements & stringency	■
A10. Post-market & ongoing monitoring	◘
A11. Treatment of uncertainty	◘
A12. Empirical basis	■
A13. Compliance & enforcement	■
A14. Incentives	■
A15. Treatment of intellectual property	◘
A16. Institutional structure	□
A17. Flexibility	◘
A18. Capacity	□
A19. Public input	□
A20. Transparency	□
A21. Attention to conflict of interest	■
A22. Informed consent	■
Extent of change	
E23. Extent of change	□
Outcomes	
O24. Public confidence	□
O25. Research & innovation	□
O26. Health & safety	◘
O27. Distributional health impacts	◘
O28. Environmental impact	■

The lead author treated the expert ratings as a starting point in developing the qualitative assessment of oversight system strengths that is reflected in Figure 3. She combined the qualitative ratings for NIH/RAC and FDA, considered levels of agreement, and further considered the history and literature discussed above. Figure 3 thus depicts a subjective rating of the 28 oversight criteria that is open to debate. As Figure 3 indicates, the two strengths noted in development of the combined oversight system were the clarity of the technological subject matter (D2) and the empirical basis of the oversight (D7). Once the combined oversight system was up and running, there were 6 strengths found: data requirements and stringency (A9), empirical basis (A12), compliance and enforcement (A13), incentives for compliance with the oversight system (A14), attention to conflict of interest (A21), and informed consent (A22). No strength was apparent in the system's extent of change and one strength was found in outcomes — attention to environmental impact (O28) in the early days of considering rDNA containment.

This is a more conservative ranking than offered by the 5 experts who piloted this ranking process. If a mean ranking of 61-100 on Figure 2 indicates a strength (see the figure's legend), then the experts agreed that clarity of technological subject matter (D2) was a strength in developing both the RAC and FDA oversight systems and agreed that the empirical basis of oversight (D7) was a strength. However, they also found financial resources (D6) a strength in development, but with a lower mean and lower level of agreement; we have not ranked this as a strength in Figure 3's qualitative assessments.

In evaluation of the attributes of the combined oversight system post-development, the expert rankings in Figure 2 agree with the Figure 3 qualitative rankings that data requirements and stringency (A9), empirical basis (A12), compliance and enforcement (A13), incentives for compliance (A14), attention to conflict of interest (A21), and informed consent (A22) are strengths. However, they also rank post-market and ongoing monitoring (A10) and treatment of uncertainty (A11) as strengths. It is difficult to see post-market review as a strength of the combined system, given the fact that no gene therapy is yet approved for marketing and that even if this is taken to mean ongoing post-approval review, the history of problems in recognizing SAEs suggests problematic post-approval review. Treatment of uncertainty, while categorized in the 61-100 range by the experts, garnered a relatively modest mean and low level of agreement.

Finally, the expert rankings agree with Figure 3's qualitative rankings in not rank extent of change (E23) as a strength and in finding the system's approach to environmental impacts (O28) a strength. However, the experts found two other outcomes to be strengths: health outcomes (O26) and distributional health impacts (O27). Figure 3 declines to rank these as strengths. Gene transfer research has had a tough time showing positive health impacts. Though there have been some relatively recent successes, no gene therapy is yet an approved therapeutic intervention, and there have been plenty of failures. With no approved therapies, it is hard to make the case for positive population impacts on health disparities.

This kind of oversight system assessment has limitations. First, our low response rate may reflect what one expert who chose not to complete the survey indicated in response to our request for participation — he did not know how to approach the survey. This new methodology may have seemed unfamiliar to a number of our respondents. Second, the community of scientists, bioethicists, lawyers, and policy makers involved in gene transfer research and its oversight is large; even with a higher response rate, the views of our experts would have been suggestive, not determinative of system assessment. Third, the wording of our criteria and survey was open to interpretation, and we cannot be sure how each expert interpreted the questions asked. Fourth, the differences between the expert responses and the qualitative evaluations reflected in Figure 3 suggest that it would be useful to interview the experts surveyed to query their responses and get a fuller sense of their evaluations.

Lessons for Nanobiotechnology

The history and evolution of gene therapy oversight offer lessons for nanobiotechnology oversight.

Using Preexisting Oversight Frameworks vs. Innovating

The gene therapy oversight story is one of oversight innovation at NIH in creating the RAC. At the FDA, gene therapy has been overseen using preexisting regulatory frameworks but with detailed attention at CBER to the specifics of this kind of gene transfer research. In contrast to both, especially the NIH innovation, authorities in the United States have generally avoided oversight innovation for nanobiotechnology so far.[269] In that respect this country is not unique — other national governments also currently lack nano-specific regulations.[270] Even at OBA, where RAC is already considering gene therapy involving nanobio, no nano-specific guidelines have yet emerged, although nano-specific guidelines have been proposed by those outside government.[271]

The federal government has only recently begun to investigate the health and safety risks of nanotechnology systematically with an eye to regulation. The National Nanotechnology Institute's (NNI) Nanotechnology Environmental & Health Implications (NEHI) Working Group was established to monitor federal research and set federal agency priorities.[272] In a 2008 report, the National Science and Technology Counsel (NSTC), through its Nanoscale Science, Engineering, and Technology (NSET) subcommittee, outlined a comprehensive strategy for researching the environmental, health, and safety (EHS) risks of nanotechnology.[273] The report identified the need to conduct EHS research to facilitate regulatory decision-making.[274] To that end, the government dedicated $58.6 million to EHS research in 2008.[275] $76.4 million more was earmarked for 2009.[276] This was only a small percentage of the $1.5 billion the federal government planned to spend on nanotechnology research in 2008.[277] By selectively funding preferred research areas, the government can effect a sort of informal regulation.[278]

While there have been calls to develop nano-specific regulatory regimes,[279] much scholarship focuses on accommodating nanotechnology within existing regulations.[280] Discussions of nanotechnology regulation have centered primarily on health and safety risks posed by consumer products rather than by research and manufacturing processes.[281] Recent work, however, has investigated how agencies such as EPA and OSHA regulate health and safety threats posed by nanoparticles released into the environment.[282] Nanobiotechnology implicates some of these same environmental release concerns. The primary concern, however, is use of nanobiotechnology in the medical context. Here, nanobiotechnology is regulated, if at all, mainly by the FDA.

Nanobiotechnology-containing products, like gene therapy products, are regulated within the same framework the FDA uses to regulate all drugs, devices, and biologics. Recognizing nanotechnology's potential to raise issues, however, the FDA published a study in 2007 investigating the adequacy and application of existing regulations.[283] The report found generally that nanoscale materials present challenges similar to, rather than fundamentally different from, products produced by other emerging technologies.[284] Indeed, the FDA repeatedly emphasized that it has "traditionally regulated many products with particulate materials in this size range."[285] The report does suggest various general regulatory changes to accommodate nanotechnology, including increasing the FDA's capacity to detect the presence of nanomaterials in products[286] and changing the regulatory pathway followed by some nanoscale materials (i.e., affecting whether they are subject to premarket approval or premarket authorization).[287]

Oversight of Real, but Uncertain Risks

Because "the risk is real for some nanotechnologies, but as yet unquantifiable,"[288] regulation of this emerging technology presents significant challenges. Gene therapy oversight provides a useful model for overseeing a young technology with potentially serious, but not yet well-characterized risks.

Nanotechnology poses potential health risks deriving not only from particle chemistry, but also from particle size, geometry, charge, and surface geography.[289] Nanoparticles have been categorized as either "incidental nanoparticles" or "engineered nanoparticles."[290] Incidental nanoparticles are naturally occurring particulates on the order of 100 nm in size, such as diesel exhaust or welding fumes, and are often irregularly shaped. Engineered nanoparticles, on the other hand, are designed to have regular shapes (spheres, tubes, rings, etc.). Recent risk research has centered on the latter.

Nanoparticles enter the body through three primary vectors — inhalation, ingestion, and through the skin.[291] Little is known about the health effects of long-term exposure to nanoparticles through any of these vectors.[292] Studies have shown that very small nanoparticles (4.6 nm in diameter) penetrate the skin's epidermal and dermal layers within 8 hours, regardless of the chemical composition of the particle coating.[293] At least one study has suggested that the particles may then be picked up and transported along neurons.[294] Particles that enter the bloodstream may "affect the blood vessel lining or function and promote blood clot formation."[295]

Nanotechnology complicates traditional models of inhaled toxins that are based solely on mass and chemical composition. Studies using chemically inert particles have shown that lung inflammation increases as the particle surface area per unit mass increases (a function of decreasing particle size).[296] The lung inflammation response varies little, on the other hand, in response to changes in mass concentration.[297] Other studies have found that nanoparticles can be transported from the nasal region to the brain through the olfactory bulb, thus bypassing the blood-brain barrier.[298] The small size of nanoparticles also makes them difficult to contain, leading to potential risks from inadvertent release of nanoparticles by research or industrial processes.[299]

The health risks associated with nanoparticles and nanostructured particles may depend on their geometric shape, in addition to their chemistry and size. Particles with widely varying nanostructure can

be purposefully manufactured, from nanosprings to nanorings, and nanobelts to nanowires.[300] Just as objects on the macro-scale interact differently with their surroundings based on their shape, so do objects on the nanoscale. The well-documented link between exposure to asbestos and increased risk of lung cancer and fibrosis has led to concern regarding inhalation of the similarly shaped carbon nanotubes. Indeed, several studies have documented lung inflammation responses in rats when exposed to single-walled carbon nanotubes (SWCNTs).[301]

The risks of exposure to nanomaterials thus seem potentially significant, but remain highly uncertain. This is analogous to the early days of human gene transfer research, when risks of human gene transfer seemed potentially serious but as yet uncertain. Oversight of gene therapy exemplifies a system that addresses uncertainty by structuring and forcing information disclosure, so that oversight bodies can assess the degree of uncertainty surrounding risks. In addition, RAC oversight exemplifies a structure that allows public review of uncertainties and risks that RAC members conclude warrant public discussion.

Oversight to Deal Flexibly with Evolving Science

Crucial to nanobio oversight will be the capacity to deal with evolving science over time. This has been a key feature of gene therapy oversight, though perhaps more evident at OBA than at the FDA. NIH oversight has evolved since initial creation of the RAC, with the emergence at different times of dedicated subcommittees and working groups. Once the science appeared more established, the role of the RAC and need for dual RAC/FDA oversight was modified. One might argue that RAC's role was too diminished in this shift, and that continuation of a more robust role might have helped avert the Gelsinger death and other SAEs that emerged. However, in fairness, after those SAEs were revealed, the RAC's role was again strengthened, though not all the way to its initial dual-approval form as in the early 1990s.

What is impressive about the chronology is not that all harm was averted — it was not. Instead, what is impressive is the oversight flexibility demonstrated in the face of changing science, data, and circumstances. Oversight for nanobio, itself a fast-changing field, will need to demonstrate a similar nimbleness.

Oversight of Ethics and Challenging Issues in Human Subjects Research

The RAC model is also extraordinary in demonstrating a capacity for sustained analysis of complex ethical and societal issues over an extended period of time. At the FDA, the primary focus has centered on safety and efficacy. At the RAC, however, ethical and societal implications have predominated.

No issue has been more important at the RAC than the protection of human participants in research. Indeed, with the emergence of human gene transfer research and establishment of RAC mechanisms to focus on the issues raised, an entire oversight structure was created to analyze risks to human subjects. Though the FDA has also assessed the acceptability and safety of protocols, RAC is striking for its focus on the questions of when the shift from animal research to human research is appropriate; how protocols should be structured, in what human subjects population, with what risks and uncertainties; how the informed consent process should proceed; and (especially post-Gelsinger) how SAEs should be handled. This is a singular model of concerted attention to the ethics, policy, and science of research in human participants. It is a powerful example of oversight for early development of new technology involving human trials. As nanobiotechnology moves into human trials, both the RAC model and the FDA's approach merit careful consideration.

Nanobio, in all likelihood, will similarly involve multiple oversight authorities, raising serious coordination issues. The need for formal harmonization and coordination efforts for the FDA and RAC at OBA should operate as a cautionary tale. Anticipating this need for nanobio by pursuing formal harmonization from the start may avert problems and even harm.

Public Access to Information

A key contrast between RAC oversight at NIH and FDA oversight has been public access to information at the former, versus protection of proprietary information through nondisclosure at the latter. Many commentators tout the public character of RAC oversight as a defining feature. Operating in public has allowed the

RAC to lead public analysis and opinion on the acceptability of gene transfer research. In addition, it has allowed the RAC to illuminate the ethical issues particular to certain forms of gene transfer research, such as germ-line gene transfer and transfer for enhancement rather than normalization. When signal events of concern have occurred, such as Gelsinger's death, the RAC has been able to address concerns publicly.

Proprietary secrecy, on the other hand, has been a problem in FDA oversight. The post-Gelsinger revelation that the FDA was aware of multiple SAEs that had not been reported publicly and shared with the RAC was profoundly unsettling and raised concerns as to whether the FDA was effectively performing its oversight job. The interest that industry had in maintaining secrecy might have played a role in why FDA became the primary regulatory body for gene therapy. In the current landscape of nanotechnology, heavy commercial involvement in both research and development suggest that implementation of a transparent regulatory scheme would require alternative mechanisms to protecting intellectual property.

Oversight Coordination

FDA/NIH coordination has been a major issue in oversight of gene transfer research. Though the two oversight systems are theoretically complementary (with FDA examining safety and efficacy, and the RAC at NIH analyzing societal and ethical implications), the reality has been less exemplary. Perhaps the nadir of coordination was the revelation post-Gelsinger that FDA was aware of SAEs that it had not shared with the RAC. Since then, harmonization efforts have hopefully improved SAE coordination between the two oversight authorities. However, their respective procedures and cultures remain quite distinct. Nanobio, in all likelihood, will similarly involve multiple oversight authorities, raising serious coordination issues. The need for formal harmonization and coordination efforts for the FDA and RAC at OBA should operate as a cautionary tale. Anticipating this need for nanobio by pursuing formal harmonization from the start may avert problems and even harm.

The Limits of Oversight Jurisdiction

A significant challenge for NIH oversight has been the limits of its jurisdiction. As noted above, NIH oversight clearly applies to federally funded research and research conducted at institutions (such as universities) rendering a general assurance that all research conducted there will comply with federal rules and oversight. However, privately funded research in private settings need not undergo RAC review. The sponsors of some of this research voluntarily subject it to RAC review, but they need not. This is in contrast to FDA review, which is required for all products whose sponsors want to market in the United States.

The private research "gap" in RAC jurisdiction is part of a broader set of issues raised by the rise of smaller commercial companies to sponsor research, sometimes by entering into relationships with academic researchers. This privatization of academic research is a broad trend in this country, encouraged by the Bayh-Dole Act.[302] However, it has raised a host of issues, including a shift in the culture of science away from public openness to proprietary secrecy and delays in publishing. As noted above, the Gelsinger case itself raised a number of these public/private, university/industry, and conflict of interest issues.

Nanobio is likely to raise the same issues — limits on oversight of private research and development, concern over the rules guiding university/industry partnerships, and difficulty coping with conflicts of interest. The history of gene therapy oversight offers not so much a model of success in wrestling these issues to the ground, but a series of cautionary tales to be considered in design of nanobio oversight.

Relationship to Politics

Oversight of human gene transfer research by the RAC and the FDA has largely shielded gene therapy from direct congressional action. Rather, an expert body at NIH and in-house analysts at the FDA have overseen this emerging technology for an extended period of time. This has allowed development of deep expertise and mastery of evolving science. It has also insulated oversight somewhat from the shifting winds of public opinion and politics. Congressional hearings and proposed legislation have at different times evidenced congressional concern, but oversight has largely been left to NIH and the FDA.

This sort of relative insulation from politics and development of deep and continuing expertise may serve nanobio oversight as well. Understanding nanotechnology is challenging, and the issues raised are complex. There is a real danger that inadequate understanding of the science and the issues raised will lead to ill-considered oversight attempts and overly reactive regulation. A model that provides some insulation from the full force of partisan politics may have the best chance to foster development of sound approaches to this still-emerging technology.

Conclusion

While the ethical issues posed by human gene transfer research and the challenges of gene therapy oversight have been much discussed, this article makes several new contributions. We systematically analyze the evo-

lution and characteristics of the gene therapy oversight system, using a range of methodologies. These include development and use of an oversight assessment survey tool that we pilot here as part of a larger project to analyze and compare oversight systems for a diversity of technologies and science domains. In this way, we help pioneer a new approach to assessing oversight of emerging technologies.

We go beyond this to focus on nanobiotechnology. We describe the ways in which nanobio approaches are being used in gene therapy and the nano-products emerging. This allows us to shed light on issues that nanobio is already beginning to raise in human gene transfer oversight.

Most importantly, we mine the gene therapy oversight experience to derive lessons for development of nanobio oversight approaches. Human gene transfer oversight has exhibited important strengths as well as significant weaknesses. As scientists, policy makers, industry, and the public struggle with the question of what oversight approaches to take to nanobio, especially in these early stages involving human subjects research in the face of marked uncertainty about risks, they have much to learn from close examination of the gene therapy oversight experience.

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88. *Id.*, at 1981-1982. Biological barriers include (1) "fastidious bacterial hosts unable to survive in natural environments; and (2) nontransmissible and equally fastidious vectors…able to grow only in specified hosts." *Id.* at 1982.
89. *Id.*
90. Berg et al., *supra* note 80, at 303; Fredrickson, *supra* note 61, at 31-32. NIH had the statutory authority to form the RAC under 42 U.S.C. § 282(b)(6), which stated that the Director of NIH

may "establish such technical and scientific peer review groups and scientific program advisory committees as are needed...." 42 U.S.C. § 282(b) (6); J. M. Rainsbury, "Biotechnology on the RAC: FDA/NIH Regulation of Human Gene Therapy," *Food & Drug Law Journal* 55, no. 4 (2000): 575-600, at 576 n.5.

91. Fredrickson, *supra* note 61, at 33. The first RAC members (by institutional affiliation and expertise) were: NIH Deputy Director for Science, Chair; Yale, molecular genetics; University of Michigan, molecular genetics; University of Alabama, microbiology; Rockefeller University, cell biology; University of Washington, microbiology; University of California at La Jolla, molecular biology; Stanford, molecular biology; Johns Hopkins, molecular biology; Brookhaven National Lab, molecular biology; University of Wisconsin, phage expert; Harvard, molecular biology; Evergreen State College, biology; Scripps Research Foundation, microbiology; Chief of Viral Diseases, National Institute of Allergy & Infectious Diseases; University of Texas, Austin, government/public affairs (added late 1975); and Georgetown University, ethics (added early 1976). *Id.*, at 34.
92. J. Areen, "Regulating Human Gene Therapy," *West Virginia Law Review* 88, no. 2 (1985): 153-171, at 156, *quoting* J. Califano, *Governing America: An Insider's Report from the White House and the Cabinet* (New York: Simon and Schuster, 1981): at 203.
93. *Id.*, *quoting* Califano, *supra* note 93, at 203 (internal quotation marks omitted).
94. Fredrickson, *supra* note 61, at 36.
95. *Id.*
96. Recombinant DNA Research Guidelines, 41 *Federal Register* 27,902 (July 7, 1976); see Fredrickson, *supra* note 61, at 39.
97. Fredrickson, *supra* note 61, at 40.
98. Fredrickson took over as NIH Director on July 1, 1975. *The NIH Almanac: Historical Data*, *available at* <http://www.nih.gov/about/almanac/historical/directors.htm> (last visited September 10, 2009).
99. Fredrickson, *supra* note 61, at 44; Recombinant DNA Research Guidelines, *supra* note 96, at 27,902. RAC went through three versions of the guidelines after Asilomar. D. S. Fredrickson, "A History of the Recombinant DNA Guidelines in the United States," in J. Morgan and W. J. Whelan, eds., *Recombinant DNA and Genetic Experimentation* (New York: Pergamon Press, 1979): at 151, *available at* <http://profiles.nlm.nih.gov/FF/B/B/K/C/_/ffbbkc.pdf> (last visited September 10, 2009) (stating that Fredrickson "could not even have explained the crucial distinctions between Federal *guidelines* and *regulations*").
100. Fredrickson, "A History of the Recombinant DNA Guidelines in the United States," *supra* note 99, at 151-152.
101. Fredrickson, *supra* note 61, at 51.
102. *Id.*, *citing* Memorandum from Susan K. Feldman to Director, National Institutes of Health, Definition and Procedures Regarding Regulations for Research on Recombinant DNA Molecules: Information (January 13, 1976) (on file with the National Institutes of Health Central Files, Com 4-4-7-1A).
103. *Id.*, at 50.
104. *Id.*, at 51.
105. Fredrickson, *supra* note 61, at 272.
106. *Id.*, at 272.
107. *Id.*
108. L. Thompson, "Human Gene Therapy: Harsh Lessons, High Hopes," *FDA Consumer Magazine* 34, no. 4 (2000): 19-24, *available at* <http://www.fda.gov/fdac/features/2000/500_gene.html> (last visited May 14, 2009).
109. Rainsbury, *supra* note 90, at 578.
110. Fredrickson, *supra* note 61, at 272-274; Rainsbury, *supra* note 90, at 578.
111. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Splicing Life: A Report on the Social and Ethical Issues of Genetic Engineering with Human Beings* (Washington, D.C.: U.S. Government Printing Office, 1982): at 3-5, *available at* <http://bioethics.gov/reports/past_commissions/splicinglife.pdf> (last visited September 10, 2009) [hereinafter *Splicing Life*].
112. *Id.*
113. *Id.*, at 3-5.
114. Hearings on Human Genetic Engineering Before the Subcommittee on Investigations and Oversight for the House Comm. on Science and Tech., 97th Cong., 2d Sess. 441-454 (November 16-18, 1982) [hereinafter Hearings on Human Genetic Engineering]; Rainsbury, *supra* note 90, at 578-581.
115. Hearings on Human Genetic Engineering, *supra* note 114.
116. Rainsbury, *supra* note 90, at 579.
117. *Id.*, at 579.
118. Office of Technology Assessment, Human Gene Therapy: Background Paper (December 1984) (on file with OTA, Washington, D.C.) [hereinafter OTA, Human Gene Therapy]; Rainsbury, *supra* note 90, at 578-581.
119. OTA, Human Gene Therapy, *supra* note 118; Rainsbury, *supra* note 90, at 578-581.
120. OTA, Human Gene Therapy, *supra* note 118; Rainsbury, *supra* note 90, at 578-581.
121. 44 *Federal Register* 17,844 (1984); Rainsbury, *supra* note 90, at 578-581; Working Group on a Response to the Splicing Life Report, April 11, 1983. On the evolution from Working Group to Human Gene Therapy Subcommittee, see National Institutes of Health, Office of Science Policy, "Gene Therapy for Human Patients: Information for the General Public," April 1990, *available at* <http://oba.od.nih.gov/rdna_rac/rac_general_public.html> (last visited May 15, 2009).
122. Rainsbury, *supra* note 90, at 578-581.
123. Human Gene Therapy Subcommittee, National Institutes of Health Recombinant DNA Advisory Committee, "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols," *DNA Technical Bulletin* 1, no. 4 (1986): 221-242 [hereinafter NIH Points to Consider].
124. See Rainsbury, *supra* note 90, at 577. DHHS had promulgated regulations for oversight of human subjects research. Areen, *supra* note 92, at 159, *citing* 45 C.F.R. § 46 (1983). At the heart of the regulations was review by the Institutional Review Board (IRB) at the researcher's home institution.
125. NIH Points to Consider, *supra* note 123; J. L. Gage, "Government Regulation of Human Gene Therapy," *Jurimetrics* 27, no. 2 (1987): 200-218, at 207-209; 50 *Federal Register* 2,942 (1985).
126. Rainsbury, *supra* note 90, at 581; T. Friedmann, P. Noguchi, and C. Mickelson, "The Evolution of Public Review and Oversight Mechanisms in Human Gene Transfer Research: Joint Roles of the FDA and NIH," *Current Opinion in Biotechnology* 12, no. 3 (2001): 304-307, 304.
127. 51 *Federal Register* 23,309 (June 26, 1986) ("Nucleic acids or viruses used for human gene therapy will be subject to the same requirements as other biological drugs.").
128. U.S. Food and Drug Administration, Center for Drugs and Biologics, "Points to Consider in Human Somatic Cell Therapy and Gene Therapy (1991)," *Human Gene Therapy* 2, no. 3 (1991): 251-256 [hereinafter FDA Points to Consider].
129. See 42 U.S.C. § 262 (a).
130. 21 U.S.C. § 321 (g) (1).
131. 21 U.S.C. § 321 (h).
132. FDA Points to Consider, *supra* note 128.
133. See Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 *Federal Register* 53,248-53,301 (October 14, 1993).
134. *Id.*, at 53,249 ("Gene therapy products are defined...as products containing genetic material administered to modify or manipulate the expression of genetic material or to alter the biological properties of living cells. Some gene therapy products...fall within the definition of biological products and are subject to the licensing provisions of the PHS Act, as well as to the drug provisions of the act.")
135. *Id.*, at II (B)(2).
136. *Id.*

137. U.S. Food and Drug Administration, "Cellular & Gene Therapy Products," *available at* <http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/default.htm> (last visited September 10, 2009).
138. Rainsbury, *supra* note 90, at 582-583.
139. *Id.*
140. R. A. Merrill, "Gene Therapy, Law, and FDA Role in Regulation," in T. H. Murray and M. J. Mehlmann, eds., *Encyclopedia of Ethical, Legal, and Policy Issues in Biotechnology*, vol. 1 (New York: John Wiley & Sons, 2000): 321-329, at 324.
141. Rainsbury, *supra* note 90, at 582-585; see also Merrill, *supra* note 140, at 324.
142. See Rainsbury, *supra* note 90, at 582-585.
143. *Id.*, at 583.
144. *Id.*, at 583-584.
145. A. B. Naumann, "Federal Regulation of Recombinant DNA Technology: Time for a Change," *High Technology Law Journal* 1, no. 1 (1986): 61-98, at 71.
146. Rainsbury, *supra* note 90, at 585.
147. *Id.*
148. Merrill, *supra* note 140, at 324.
149. See Rainsbury, *supra* note 90, at 585-586; see also Merrill, *supra* note 140, at 324.
150. Rainsbury, *supra* note 90, at 586.
151. Merrill, *supra* note 140, at 325.
152. Rainsbury, *supra* note 90, at 586.
153. *Id.*, at 586.
154. P. D. Noguchi, "From Jim to Gene and Beyond: An Odyssey of Biologics Regulation," *Food & Drug Law Journal* 51, no. 3 (1996): 367-373, 369.
155. National Institutes of Health, Recombinant DNA Research: Actions under the Guidelines, 60 *Federal Register* 20,726 (April 27, 1995). See also 62 *Federal Register* 4,782 (January 31, 1997); Noguchi, *supra* note 154, at 369-370.
156. Noguchi, *supra* note 154, at 369.
157. *Id.*
158. See Rainsbury, *supra* note 90, at 588 ("External pressure on NIH to eliminate the RAC, or at least to streamline RAC's review process, was predicated largely on the assumption that dual FDA/RAC investigation of clinical protocols was a rate-limiting step in the development of novel genetic therapies.").
159. National Institutes of Health, Recombinant DNA Research: Notice of Intent To Propose Amendments to the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) Regarding Enhanced Mechanisms for NIH Oversight of Recombinant DNA Activities, 61 *Federal Register* 35,774 (July 8, 1996).
160. Fredrickson, *supra* note 61, at 286.
161. Friedmann, Noguchi, and Michelson, *supra* note 126, at 305.
162. Merrill, *supra* note 140, at 328 (noting that of the 61 comments the NIH received addressing the proposal to eliminate the RAC, 41 were opposed).
163. 62 *Federal Register* 4,782 (January 31, 1997).
164. Friedman, Noguchi, and Michelson, *supra* note 126, at 305.
165. *Id.*
166. 62 *Federal Register* 59,032 (October 31, 1997).
167. On FDA authority, see U.S. Food and Drug Administration, *supra* note 137; see also Merrill, *supra* note 140, at 322.
168. Merrill, *supra* note 140, at 328.
169. See NIH Guidelines for Research Involving Recombinant DNA Molecules (April 2002) Appendix M-1-C-4, *available at* <http://oba.od.nih.gov/rdna/nih_guidelines_oba.html> (last visited September 10, 2009) [hereinafter NIH Guidelines, 2002].
170. L. Smith and J. F. Byers, "Gene Therapy in the Post-Gelsinger Era," *JONA's Healthcare Law, Ethics, & Regulation* 4, no. 4 (2002): 104-110, at 104.
171. *Id.*
172. N. Somia and I. Verma, "Gene Therapy: Trials and Tribulations," *Nature Reviews Genetics* 1, no. 2 (2000): 91-99, at 95.
173. D. T. Zallen, "U.S. Gene Therapy in Crisis," *Trends in Genetics* 16, no. 6 (2000): 272-275, 274.
174. J. Silberner, "A Gene Therapy Death," *Hastings Center Report* 30, no. 2 (2000): 6.
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177. *Id.*
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179. Zallen, *supra* note 173, at 274.
180. Rainsbury, *supra* note 90, at 594.
181. 65 *Federal Register* 60,328 (October 10, 2000).
182. See Note, "Guiding Regulatory Reform in Reproduction and Genetics," *Harvard Law Review* 120, no. 2 (2006): 574-596, 580 (observing that the RAC "serves as a deliberative body for considering novel ethical questions raised by new types of gene transfer research").
183. Friedmann, Noguchi, and Michelson, *supra* note 126, at 305.
184. Only about 20-30% of submitted protocols are selected for public review. See N. M. P. King, "RAC Oversight of Gene Transfer Research: A Model Worth Extending?" *Journal of Law, Medicine & Ethics* 30, no. 3 (2002): 381-389, at 385.
185. *Id.*
186. Friedmann, Noguchi, and Michelson, *supra* note 126, at 306.
187. King, *supra* note 184, at 385.
188. See Friedmann, Noguchi, and Michelson, *supra* note 126, at 306.
189. K. Cornetta and F. O. Smith, "Regulatory Issues for Clinical Gene Therapy Trials," *Human Gene Therapy* 13, no. 10 (2002): 1143-1149, 1146.
190. See 66 *Federal Register* 57,970 (November 19, 2001).
191. See Coronetta and Smith, *supra* note 189, at 1146; see also NIH Guidelines 2002, *supra* note 169 ("Principal Investigators must submit, in accordance with this section...a written report on: (1) any serious adverse event that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product; investigators should not await definitive proof of association before reporting such events)."). See also 21 C.F.R. 312.32 (c) (1) (outlining the FDA's SAE reporting requirements).
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203. *Id.*
204. See 42 U.S.C. § 262 (a).
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207. FDA/CBER, Human Gene Therapy and the Role of the Food and Drug Administration, *available at* <http://www.fda.gov/cber/infosheets/genezn.htm> (last visited May 22, 2009).
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220. Marshall, *supra* note 216, at 320; Cornetta, *supra* note 219, at 53.
221. Recombinant DNA Advisory Committee, Minutes of Meeting (February 10, 2003), at 3, *available at* <http://www4.od.nih.gov/oba/RAC/minutes/RAC_minutes_02-03.pdf> (last visited May 19, 2009).
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244. *Splicing Life, supra* note 111, at 82-88.
245. L. Walters and J. G. Palmer, *The Ethics of Human Gene Therapy* (New York: Oxford University Press, 1997): at 148.
246. *Id.*, at 151.
247. *Id.*, at 147-152.
248. *Id.*, at 151.
249. King, *supra* note 184.
250. *Id.*, at 386.
251. S. M. Wolf, "Ban Cloning? Why NBAC Is Wrong," *Hastings Center Report* 27, no. 5 (1997): 12-15.
252. See, e.g., King, *supra* note 184, at 381-382.
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260. See Croley, *supra* note 259.
261. M. S. Garfinkel et al., *Synthetic Genomics: Options for Governance*, October 2007, *available at* <http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf> (last visited September 10, 2009).
262. *Id.*, at 42-44.
263. Kessler et al., *supra* note 257, at 1735.
264. FDA Science Board, Subcommittee on Science and Technology, *FDA Science and Mission at Risk*, November 2007.
265. *Id.*, at 24, 27.

266. See J. Kuzma et al., "An Integrated Approach to Oversight Assessment for Emerging Technologies," *Risk Analysis* 28, no. 5 (2008): 1197-1220, at 1217. The survey is available in the online version of the article. *Id.*
267. J. Paradise et al., "Developing U.S. Oversight Strategies for Nanobiotechnology: Lessons from Past Oversight Experiences," *Journal of Law, Medicine & Ethics* 37, no. 4 (2009): 688-705.
268. See B. C. Karkkainen, "Information as Environmental Regulation: TRI and Performance Benchmarking, Precursor to a New Paradigm?" *Georgetown Law Journal* 89, no. 2 (2001): 257-370, at 287.
269. See A. C. Lin, "Size Matters: Regulating Nanotechnology," *Harvard Environmental Law Review* 31, no. 2 (2007): 349-408, at 361.
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275. *Id.*, at 44.
276. *Id.*
277. Chemical & Engineering News, "Nanotech Strategy: Prioritizing Federal Efforts for Studying Health and Safety of Nanomaterials Evolves," *available at* <http://pubs.acs.org/cen/government/86/8609gov2.html> (last visited September 10, 2009).
278. See G. E. Marchant and D. J. Sylvester, "Transnational Models for Regulation of Nanotechnology," *Journal of Law, Medicine & Ethics* 34, no. 4 (2006): 714-725, at 714.
279. See, e.g., Lin, *supra* note 269, at 351 ("[N]anotechnology poses distinct and serious concerns that warrant legislation specific to the manufacture and use of nanomaterials."); Marchant and Sylvester, *supra* note 276, at 723 (discussing transnational regulation, and finding that "nanotechnology will likely require its own unique approach").
280. See, e.g., J. C. Davies, "Managing the Effects of Nanotechnology," Woodrow Wilson International Center for Scholars, January 2006, at 10 (while noting that new regulatory frameworks may be needed, describing only how current regulatory law can be applied to nanotechnology); P. J. Tomasco, Note, "Manufactured Nanomaterials: Avoiding TSCA and OSHA Violations for Potentially Hazardous Substances," *Boston College Environmental Affairs Law Review* 33, no. 1 (2006): 205-245, at 238.
281. See M. Greenwood, "Thinking Big About Things Small: Creating an Effective Oversight System for Nanotechnology," March 2007, at 10, *available at* <http://www.nanotechproject.org/file_download/files/Greenwood%-%2OPEN%207.pdf> (last visited May 15, 2009).
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283. FDA, *Nanotechnology: A Report of the U.S. Food and Drug Administration*, July 25, 2007, at 4, *available at* <http://www.fda.gov/nanotechnology/taskforce/report2007.pdf> (last visited September 10, 2009).
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288. A. D. Maynard, "Nanotechnology: Assessing the Risks," *Nano Today* 1, no. 2 (2006): 22-33, at 32.
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291. Maynard, *supra* note 288, at 24.
292. See *id.*, at 31 ("[S]pecific information on hazard, exposure, dose, response, and other compartments within risk assessment frameworks is lacking.")
293. J. P. Ryman-Rasmussen et al., "Penetration of Intact Skin by Quantum Dots with Diverse Physicochemical Properties," *Toxicological Sciences* 91, no. 1 (2006): 159-165.
294. G. Oberdorster et al., "Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles," *Environmental Health Perspectives* 113, no. 7 (2005): 823-839.
295. Maynard, *supra* note 288, at 27.
296. C. L. Tran et al., "Inhalation of Poorly Soluble Particles. II.: Influence of Particle Surface Area on Inflammation and Clearance," *Inhalation Toxicology* 12, no. 12 (2000): 1113-1126.
297. *Id.*
298. See G. Oberdorster et al., "Translocation of Inhaled UIltrafine Particles to the Brain," *Inhaled Toxicology* 16, nos. 6/7 (2004): 437-445, at 441; A. Elder et al., "Translocation of Inhaled Ultrafine Manganese Oxide Particles to the Central Nervous System," *Environmental Health Perspectives* 114, no. 8 (2006): 1172-1178.
299. See A. Maynard and E. D. Kuempel, "Airborne Nanostructured Particles and Occupational Health," *Journal of Nanoparticle Research* 7, no. 6 (2005): 587-614.
300. See Z. L. Wang, "Nanostructures of Zinc Oxide," *Materials Today* 7, no. 6 (June 2004): 23-33 (illustrating the synthesis of a wide variety of nanostructures from ZnO).
301. See, e.g., D. B. Warheit et al., "Comparative Pulmonary Toxicity Assessment of Single-Wall Carbon Nanotubes in Rats," *Toxicological Sciences* 77, no. 1 (2004): 117-125; V. E. Kagan et al., "Nanomedicine and Nanotoxicology: Two Sides of the Same Coin," *Nanomedicine: Nanotechnology, Biology and Medicine* 1, no. 4 (2005): 313-316.
302. 35 U.S.C. §§ 200-212.