Commentary: Who's Afraid of the RAC? Lessons from the Oversight of Controversial Science

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As Susan Wolf and her co-authors ably outline in their article in this symposium, the system of oversight of recombinant DNA (rDNA) technology has evolved as a function of and response to various factors, from scientific to policy related to political.[1] In this commentary, I would like to briefly address what we might call a Goldilocks question: When it comes to dealing with controversial new biomedical technologies, is an oversight regime like that applied to gene transfer research too little oversight, too much, or just right? Or do we need something different than the porridge we've been making for the last 30 years? As a matter of disclosure, I am currently a member of the National Institutes of Health's (NIH) Recombinant DNA Advisory Committee (RAC), but these views are my own and do not represent a position of the RAC, any other member of the committee, or the NIH.

I have great respect for the work done by the RAC and the Food and Drug Administration (FDA) in oversight of human gene transfer research. But that good work comes at some cost. There is a strong case to be made that human gene transfer trials are the single most heavily regulated area of biomedical research. In addition to separate (and coordinated) oversight by the FDA and the RAC as outlined by Wolf et al., gene transfer research must also be reviewed and approved by local Institutional Biosafety Committees (IBCs) and Institutional Review Boards (IRBs).[2] These multiple layers of review and oversight are due to the trials being a combination of recombinant DNA research and research on human subjects. Oversight of rDNA research in plants or animals is limited to IBCs in the case of plants and IBCs plus institutional animal care and use committees (IACUCs) in the case of animals. Clinical trials that do not involve gene transfer are reviewed by IRBs (with FDA review in the case of a desire for approval of a new drug, device, or biologic). So, we might ask, what have been the effects and impacts of such heavy oversight and control? None other than Donald Fredrickson, the Director of NIH for an important part of the history of oversight of rDNA research and the official who chartered the RAC, has written that early efforts may have gone too far: "Faced with real questions of theoretical risks, the scientists paused and then decided to proceed with caution. That decision gave way to dangerous overreaction and exploitation, which gravely obstructed the subsequent course."[3] For Fredrickson, however, the overabundance of caution was necessary and appro-

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priate: "Uncertainty of risk, however, is a compelling reason for caution. It will occur again in some areas of scientific research, and the initial response must be the same. After that the lessons learned here should help us through the turbulence that is sure to come."[4]

As Wolf et al. note, the risks of nanobiotechnology seem significant but with a great amount of uncertainty.[5] Thus, caution would seem to be the rule of the day. Concern over both the likelihood and magnitude of risks was not the only reason for the scientific community to exercise caution in the area of rDNA. An interesting aspect of the story of rDNA research and its oversight is that an important goal of the scientific community in addressing the issues raised by rDNA technology was to blunt the need for government oversight — something of an attempt by the community to regulate itself before the government decided to do it to them. Whatever one thinks of the community's concerted efforts at the Asilomar conference and later meetings, it did not seem to lead to lighter-handed regulation and oversight of the science either initially or as the area of science evolved.

As Wolf et al. note, one of the reasons for intense focus on oversight of gene transfer research in later years was the death of a research subject in the person of Jesse Gelsinger, and the gaps in some aspects of reporting and oversight that were exposed in the aftermath of that case. Rightly or wrongly, one of the general assessments of the state of gene transfer research post-Gelsinger was that it was a technology in which investigators were overestimating potential benefits, the media was hyping its curative potential, and oversight mechanisms struggled to keep up with both.[6] If this assessment sounds familiar, it should. It bears a striking resemblance to the way many have characterized the human embryonic stem cell (hESC) research debate.

But while human gene transfer research continues to receive heavy regulation and oversight, the oversight of hESC research has at least until now taken a different path. When the Bush administration made the decision to limit federal funding for hESC research to existing cell lines in August 2001, it had implications for more than the investment of the federal government in a new and controversial area of biomedical research. By restricting federal spending, the decision limited the reach of federal oversight (and thus control) of this area of research. This is due to the fact that the president (through Executive Orders) and Executive Branch agencies (through the regulatory process) can make rules for research carried out within or funded by Executive Branch agencies, where NIH and many other research agencies reside. But they cannot make rules for research performed or funded outside of the Executive Branch, most importantly research in the private sector. Rules for non-federally funded research, including all research performed with private funding, require the passage of legislation by Congress and subsequent signing into law by the president — a much more politically challenging prospect. The converse of this point is also critically important. The decision to institute a federal oversight regime through the Executive Branch requires federal funding. Since the federal government of the United States is by far and away the largest funder of science research in the world, the decision to fund and therefore create oversight in an area of science (or in the reverse order) is arguably the difference between the growth and languishing of an area of scientific research.

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To return to the initial question I posed: — does the oversight of human gene transfer research represent too little, too much, or just the right approach? Clearly there are lessons to be learned from this experience that are important for whichever tack is taken for oversight of nanobiotechnology:

- Government oversight and investment go hand in hand. Without investment by the government, the reach of agency oversight is necessarily limited. This is a unique feature of American civics, and a point that cannot be overlooked in consideration of oversight and control of new areas of science.
- Proactive and prospective discussion is critical, with flexibility in subsequent implementation. The history of the development of rules and oversight for rDNA research and eventual gene transfer trials in humans is about nothing if not about attempts at careful and proactive discussion. As

the history of rDNA research makes clear, nobody has the proverbial crystal ball to predict the future of research and requisite oversight to go with it. For that reason, oversight policy and practice must evolve with the science. This has been an important lesson of RAC and FDA oversight of gene transfer research and will be important to keep in mind as nanobiotechnology develops.

- The right mix of diverse stakeholders at the table is important. Part of the story of oversight of rDNA and gene transfer research is that there were multiple stakeholder perspectives represented during policy discussions about an area of new and controversial science. While the discussion started within the scientific community, it expanded to include voices representing environmental, ethical, theological, and even historical perspectives. This diversity led to the healthy and vigorous debate that was critical to successful policy making. We could do worse than follow a similar recipe when considering oversight of nanobiotechnology and other areas.
- Transparency and accountability are crucial for building and maintaining trust. The combination of regulatory (e.g., FDA) and advisory (e.g., RAC) oversight has the strength of regulatory accountability coupled with the transparency and openness of a public advisory process. While such a combination may create some overlap, redundancy, and even friction, those same features help foster and preserve public trust.
- Do not let the hype get ahead of the science. If nothing else, the history of gene transfer research should have taught us humility in our expectations. The applications of gene transfer technologies have seen limited therapeutic success, though the science and its results continue to improve. Thus a proper balance needs to be maintained between the potential benefits and possible risks of new technologies, not least in the portrayal of information related to the recruitment of human subjects into trials and the process of informed consent. As we continue to hear announcements and read stories of the vast potential for human embryonic stem cells, it will serve us well to keep these lessons in mind.

The combination of caution, multi-level oversight, broad participation, and mechanisms for public accountability has contributed to the continued progress in rDNA research. There could have been alternate paths taken, leading to alternate histories — irresponsible behavior, limitations on funding, or outright prohibitions — all of which would likely have set back or even led to the demise of the rDNA research. On the flip side, less rigorous (some might argue less onerous) oversight may have allowed more rapid advancement and the hoped-for widespread therapeutic applications that have so far eluded human gene transfer. We have clearly taken the middle path, and for the oversight of new and controversial science, such a balance seems just right.

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References

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2. *Id.*
3. D. S. Fredrickson, *The Recombinant DNA Controversy* (Washington, D.C.: American Society of Microbiology Press, 2001): at 278.
4. *Id.*
5. See Wolf et al., *supra*, note 1.
6. C. Scott, "What Stem Cell Therapy Can Learn from Gene Therapy," *Nature Reports Stem Cells* (2008), published online September 4, 2008.