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How Federal Science Agencies Innovate in the Public Interest

A unique class of scientist-bureaucrats at the National Cancer Institute shows that government science is an asset we can't afford to lose.

Like many scholars of federal science policy, I awaited the Supreme Court's ruling in *Loper Bright Enterprises v. Raimondo* with some trepidation. When it came down on June 28, 2024, the decision overturned the *Chevron* doctrine, which for four decades held that courts could defer to the interpretations of expert government agencies when congressional statutes are ambiguous. Defenders of the nation's many expert regulators expressed concern that the *Loper Bright* decision will hobble the federal government's ability to protect citizens from potential harms by sidelining the judgment of experts in favor of the courts.

While philosophies of governance vary, there is sound political theory behind the practical strategy of delegating policy decisions to expert civil servants in federal agencies. Legislators and their staffs often lack the technical expertise to fully specify the ins and outs of legislation that deals with complex matters of science and technology governance (so, it is worth noting, do the courts). While much of the discussion around *Loper Bright* has focused on regulatory agencies such as the US Environmental Protection Agency and the Food and Drug Administration, the potential impact on federal agency authority goes much further.

Many important expert agencies in the federal government are not regulatory at all, but instead are oriented toward missions that involve them in the production and development of science and technology with far-reaching political and economic consequences. Among these mission-oriented federal science agencies, the National Cancer Institute (NCI) offers a compelling illustration of why allowing expert scientists the discretion to broadly interpret their agency's statutory mission enables not only sound policy, but a brand of scientific innovation marked by a distinct commitment to serving the public good.

The National Cancer Institute is the largest single patron of cancer research in the United States. As part of the National Institutes of Health (NIH), the NCI is chartered with a dual mission: first, to sponsor research into the causes of cancers; and second, to apply the results of such research to the treatment and amelioration of these diseases. Today the NCI is best known for its role in awarding grants to external academic researchers studying fundamental biological mechanisms and testing clinical treatments for cancer. But one of the most fascinating dimensions of the agency's history can be found in its intramural, or in-house, scientists' expertise in cancer virus research and vaccine innovation. As a consequence of their scientific successes, many of these intramural researchers rose to positions of bureaucratic leadership, where they participated in administrative governance and crafted policy alongside their day-to-day scientific research.

Wearing both scientific and bureaucratic hats, the NCI's hybrid "scientist-bureaucrats" came to interpret their research projects through the administrative work they did to serve the NCI's dual mission, and vice versa. The close interconnection between scientific and bureaucratic practices allowed NCI actors to develop distinct policy expertise that profoundly shaped the trajectory of biomedical research innovation and governance in the United States toward public health-relevant science. In crucial instances, NCI scientist-bureaucrats leveraged the agency's mission to create new policies and programs to help develop life-saving innovations and distribute them to populations in need.

It is precisely this kind of bureaucratic discretion that the *Loper Bright* decision (and other movements to limit the authority of federal civil servants) now threatens to undermine. As dissenting justices argued, *Loper Bright*

returns administrative agencies to a pre-*Chevron* world where routine policymaking could become a "font of uncertainty and litigation"—a world where the policies that led to some of the NCI's most celebrated bureaucratic and scientific innovations would be impossible.

Leading the translational charge

The policy paradigm of "translational research" in biomedicine—that is, the notion that fundamental "benchside" research should be developed into useful tools for treating patients at the "bedside"—found an early champion in Samuel Broder of the NCI's intramural Clinical Oncology Program. Early in the HIV/AIDS epidemic, Broder helped lead a collaborative effort between intramural laboratory scientists and clinical researchers to rapidly identify antiretroviral candidates and move them into clinical trials.

Broder's work was instrumental to the development and testing of nucleoside analogs, the first class of drugs (including AZT and ddI) that effectively combatted HIV/AIDS. Broder considered the presence of so many intramural scientists and clinicians in close proximity to one another on the NIH campus, all working in service to a public health mission, critical to the ability to move knowledge and materials between bench and bedside early in the HIV/AIDS epidemic.

When he was appointed director of the NCI in 1989, Broder brought his distinctive philosophy of translational research to bear on the agency's dual mission to support science and improve health. Broder firmly believed that the flow of knowledge between lab and clinic should be bidirectional, and drew upon his experiences in HIV/AIDS drug development to lay the groundwork for a nationwide translational research infrastructure. Looking at extramural grant mechanisms, to which the majority of the NCI's budget is allocated, Broder flexed his bureaucratic muscle to forge new funding mechanisms specifically designed to nurture translational collaborations in the academic community. He rehabilitated multidisciplinary P01 project grants, which support groups of investigators, as collaborative translational alternatives to the oft-siloed individual investigator R01 grant. He also oversaw development of the Specialized Programs of Research Excellence (SPORE) grant, which established multidisciplinary centers dedicated to translational research on some of the most common cancers in hospitals throughout the nation. Translational P01 and SPORE grants challenged the status quo favoring basic research and emphasized the NCI's mandate to ameliorate the national burden of cancer.

Broder also had a vision for translational research in the intramural program. He had been disillusioned over his experience with private industry drug development during the HIV/AIDS epidemic; though Broder and his colleagues had been largely responsible for the development and testing of AZT, the pharmaceutical company Burroughs Wellcome had gone on to claim full patent rights for the drug. Leveraging their control over the patent, Burroughs Wellcome set an exorbitant price for AZT that galled public health advocates—sometimes into overt protest.

Learning from these bitter experiences with AZT drug development, Broder envisioned the NCI as an alternative "'pharmaceutical company' working for the public" and not private profit. He pushed for patenting and licensing reforms throughout the NIH that would ensure innovations developed by intramural scientists would be competitively licensed so their prices could be affordable enough to benefit the global populace.

Biomedical innovation as a public good

A test for this vision of intramural translational research came in the form of a new vaccine against the human papillomavirus (HPV). The HPV pathogen is responsible for the majority of cervical cancers and many other anogenital and head and neck cancers. John Schiller and Douglas Lowy of the NCI's intramural Laboratory of Cellular Oncology made an important breakthrough in 1991, when they demonstrated that one of the virus's harmless outer proteins could be made into a safe and efficacious subunit vaccine, delivering only small portions of a microbe into the body in order to elicit an immune response without introducing any of the microbe's disease-causing genes. As Schiller and Lowy noted early in human trials, "an effective HPV vaccine may have a greater potential for reducing worldwide cancer burden than any other currently conceived anticancer program."

However, producing the vaccine at scale required overcoming several barriers. A major one was that only the private sector has the capacity to produce vaccines at market scale. This meant that Schiller and Lowy's HPV vaccine—like Broder's nucleoside analogs before them—would have to be licensed to a private company for commercial development if it would ever see the light of day.

However, Broder's earlier experiences had influenced the way the HPV patent was developed. Broder and the NIH legal team were determined to improve the government's approach to intellectual property to better ensure the public, and not merely private firms, would benefit from federal innovation. They developed a patent-licensing policy that stipulated patents developed by federal scientists working at NIH must be licensed to multiple private companies. The principle of nonexclusive licensing for NIH-owned intellectual property was intended to drive down drug prices by putting private companies into competition with one another. At a time when direct government intervention in drug prices was considered a political nonstarter, competitive co-licensing agreements were seen as one of the most effective strategies federal agencies could leverage to lower drug prices while ensuring private companies would translate new discoveries into scalable medical interventions.

Schiller and Lowy's HPV vaccine technology was co-licensed to Merck and MedImmune (which transferred its license to GlaxoSmithKline soon after human trials began). Schiller and Lowy decided to continue independent research on the vaccine, teaming up with colleagues in the NCI Division of Cancer Epidemiology and Genetics to conduct intramural trials to run in parallel with those conducted by the pharmaceutical companies. NCI scientists were concerned that either of the companies could make business-related decisions to discontinue clinical trials for the vaccine for any number of reasons the NCI inventors had no control over.

Furthermore, Schiller and Lowy suspected that information gleaned from the clinical application of their laboratory's findings could inform further research that might improve cancer outcomes in the future. Their decision to conduct NCI-sponsored clinical trials thus reflected their investment in the NCI's dual mission: on the one hand, they believed that knowledge obtained from these trials could improve research on the virus and its disease manifestations; and on the other hand, they wanted to ensure the vaccine would be available as a global public health tool whether industry found it profitable or not.

Whereas the pharmaceutical companies conducted phase II and III trials of their branded HPV vaccines on adolescents in high-income countries, the intramural NCI clinical trials took place in Costa Rica. This location allowed NCI scientists to orient their vaccine research toward the women in low- and middle-income countries who bore the overwhelming burden of HPV-related cervical cancer morbidity and mortality—in part because of the difficulty of providing regular Pap screenings in low-resource settings.

Yet the very things that made routine Pap screening a suboptimal public health strategy in areas that lacked health care infrastructure also frustrated the original HPV vaccine delivery schedule. A recombinant subunit technology that required cold chain storage for three doses to be administered over 9–12 months proved difficult to implement in low-resource settings.

Recognizing these hurdles, the NCI team found value in tracking women who did not complete the three-shot protocol rather than dropping them from the study, as drug companies are wont to do. Following these women revealed whether the vaccine was sufficiently immunogenic to require fewer shots, thus reducing the vaccine's burden on patients and providers in low-resource settings. The NCI team's follow-ups soon demonstrated that even women who received only the first shot of the three-shot protocol showed an immune response sufficient to suggest protection against the targeted HPV strains several years after administration.

Their findings led Schiller and Lowy to advocate for further research into a one-shot protocol for the first-generation vaccine as the most logistically practical and cost-effective alternative for vaccinating populations in developing countries. Based on the NCI's findings and mounting evidence from other trials conducted in low- and middle-income countries, the World Health Organization recommended adopting a single-shot HPV vaccine regimen in 2022.

Making good on a dual mission

For NCI leadership, the story of HPV vaccine innovation was a translational triumph. It illustrated, according to NCI director John Niederhuber, how "basic discoveries arising from population studies, molecular biology, and immunology can be rapidly translated through public and private research efforts to solve significant public health problems, and in this case, perhaps the elimination of cervical cancer as a threat to women's health." The role NCI scientists, clinicians, and epidemiologists played in inventing the enabling technology and testing it in under-resourced populations illustrates how NCI scientists combine a commitment to producing knowledge about cancer with a motivation to improve public health—especially in instances where they believed private interests would prioritize profit over the global population's needs.

At a time when funding for extramural NCI grants is ever-shrinking, some scientists question the value of maintaining an intramural research program that consumes 16–18% of the agency's budget every year. Yet the value of the NCI's intramural program is greater than the research it conducts: it also encompasses the training of hybrid scientist-bureaucrats who are able to develop agency policies and scientific projects that would otherwise be impossible. Straddling the standards of the scientific community and the demands of federal science policy, the NCI's scientist-bureaucrats are vital to the agency's ability to cultivate science and policy that serve the public interest. By elevating researchers whose work has enhanced public health to leadership positions, the NCI has ensured that congressional investments in science are directed not only toward promising fundamental research, but also toward the ultimate end of improving human health.

Knowledgeable and publicly accountable policymaking is an art that scientist-bureaucrats learn by doing, making the NCI's intramural program a vital incubator for both the experts and the policies that help make the nation's cancer research effort thrive. This arrangement is one we stand to lose at our own peril. While science policies are never perfect, they are better when they are informed by the experiences of such mission-driven experts who have committed themselves to the betterment of science and the public good.

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