Situated practice and the emergence of ethical research: HPV vaccine development and organizational cultures of translation at the National Cancer Institute

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ABSTRACT

This paper explores the role scientists at the National Cancer Institute (NCI), a US federal science agency, played in researching and testing vaccines for the human papillomavirus (HPV). Drawing upon archival sources and oral history interview data, I challenge accepted narratives that attribute the design of HPV vaccines to profit motive, instead showing that pharmaceutical companies developed early protocols and enabling technologies designed by government researchers. I argue that interpretations of "translational research" native to the NCI influenced these researchers' efforts to design and test first- and second-generation HPV vaccines. These understandings form part of a broader organizational culture that positions the NCI as a countervailing and supplementary force in the field of translational research and development (R&D). NCI researchers' conceptions of the Institute's role allowed them to develop an understanding of ethical HPV vaccine research as oriented toward addressing cervical cancer health disparities, especially in developing nations. NCI scientists' understanding of their role in

serving the public good through continued HPV vaccine innovation reflects their situatedness in the political economy of R&D through the lens of this organizational culture.

Key words: politics, power, governance; HPV; ethics

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"Translational research" is a buzzword commonly used to describe the tortuous process whereby discoveries made at the laboratory bench are brought to bear on medical interventions at the patient's bedside. The increasingly complex relationships between academy, industry, and government that sustain translational research initiatives have led many STS scholars to consider translational research in light of a shift toward neoliberal regimes of science policy, whereby market influences colonize domains of research and development (R&D) previously populated by publicly-supported science (see Maienschein et al. 2008; Sunder Rajan and Leonelli 2013). As Elizabeth Popp Berman (2014) notes, narratives that attempt to unify recent policy trends toward economizing science as "neoliberal" gloss over the complexity of actual policy initiatives, many of which contain strong critiques of market failure. At a time when the institutional environment of universities make these organizations increasingly isomorphic with private firms (Hackett 1990), policymakers view government science as fulfilling a role that market forces fail to adequately address.

Not only do scientists and policymakers at government organizations like the National Cancer Institute (NCI) perceive industry as reluctant to adequately invest in basic research and cancer drug development, they also argue that private R&D efforts can undermine the public good. To the extent the NCI's translational research initiatives critique and even challenge the market's role in R&D, they do not square neatly with narratives of translational research as neoliberal science policy. The primary assumptions of a neoliberal framework, that public science is being marketized for private profit, must be qualified in the face of countervailing

trends that allow federal agencies to impose patenting, licensing, usage, and pricing restrictions upon drugs developed from government discoveries.

I call into question the idea that profit concerns primarily motivated decision-making around research and clinical testing for first-generation HPV vaccine technology. Drawing upon archival sources and oral history interviews[1] that chronicle the activities of NCI scientists involved in translational HPV vaccine research, I argue the NCI's organizational culture of translation shaped the possibilities for conceiving and developing ethical HPV vaccines. The NCI's organizational culture of translation allowed researchers to imagine themselves as offering countervailing or supplementary approaches to HPV vaccine development and testing as they imagined it to proceed in industry.

SOCIAL AIMS IN HPV VACCINE PRODUCTION

In 2006, a landmark innovation in cancer research was approved by the US Food and Drug Administration (FDA) for public use. The polyvalent subunit vaccine, marketed as Gardasil by Merck and Cervarix by GlaxoSmithKline (GSK), targeted up to four strains of the human papillomavirus by eliciting immune responses to one of the viruses' non-oncogenic structural proteins, L1. Touted as the first technology to effectively protect users from cervical cancer, these vaccines inoculated against the two "high-risk" strains (HPV-16 and 18) associated with

[1] Documentary evidence was sourced from the National Archives and Records Administration II (NARA II) at College Park, MD; General Collections of the National Library of Medicine at Bethesda, MD; modern manuscripts and personal papers of the History of Medicine Division of the National Library of Medicine at Bethesda, MD; and the Library of Congress at Washington, D.C. I also consulted digital archives of the National Cancer Institute, the Food and Drug Administration, the Government Printing Office, and Archive.org. I collected oral history interview data from the Office of NIH History's Oral History Archive and the oral history archives at the History of Medicine Division of the National Library of Medicine. As no direct accounts of HPV vaccine development are included in these archives, I supplement these oral history data with evidence from interviews I conducted with John Schiller in 2015 and Douglas Lowy in 2017.

the vast majority of cervical cancers in the US. Historians and sociologists of science have studied the complex political and cultural dimensions of HPV vaccination and associated cervical cancer prevention regimes (Casper and Carpenter 2008; Löwy 2011; Mamo and Epstein 2014; Wailoo et al. 2010). However, few scholars have investigated the R&D processes that led to the L1 virus-like particle (VLP) technology that made the vaccines possible.

The exception is an account by bioethicists Kristen Intemann and Immaculada de Melo-Martín (2010). Herein the authors argue that social values of clinical trial *efficacy* (safe and acceptable reduction in disease markers) prevailed in shaping Gardasil as a vaccine technology and a public health intervention. The vaccine's active ingredient, the L1 VLPs, must be produced in a sensitive eukaryotic growing medium that requires refrigeration. This makes the vaccine costly at $360 over a three-dose regimen. While the use of L1 VLP technology and the three-dose regimen ensured the vaccine would prove immunogenic in clinical trials, it also ensured that the vaccine would be most easily accessible to first-world women of means.

Considerations of efficacy served the interests of pharmaceutical companies who "aim[ed] to produce a profitable vaccine" (Intemann and Melo-Martín 2010:207), but did little to reduce the global burden of HPV disease. Had these scientists been instilled with social aims of *efficiency* in disease reduction rather than clincal trial efficacy, the authors argue, they could have drawn from a universe of possible vaccine technologies that were cheaper, shelf-stable, and thus more likely to reduce the burden of cervical cancer among the poor, rural women in developing nations who account for over 80% of all cervical cancer deaths worldwide.

According to Intemann and Melo-Martín, the social aims of research should be more openly considered alongside its epistemic aims. The authors suggest that the social aims of getting a profitable vaccine to market quickly led HPV vaccine researchers to conduct clinical

trials that did not take the needs of women in developing nations into consideration. They also led vaccine manufacturers to ignore alternative vaccine technologies that had been proposed by 2006. These alternatives included naked DNA vaccines that delivered HPV DNA directly to the system; vaccines using live attenuated bacterial vectors that produced recombinant L1 VLPs; or transgenic plants that expressed VLPs and could be delivered orally. Each of these alternatives promised to resolve one or more of the key issues restricting access by eliminating either the need for refrigeration, multiple doses, or high cost.

However, historical evidence suggests NCI scientists *had* tested the vaccine alternatives Intemann and Melo-Martín propose as possible with an aim to offer cheaper and more stable vaccine alternatives "for widespread distribution in developing countries, where most cervical cancers occur" (Schiller and Nardelli-Haefliger 2006:S147). However, these alternatives proved too underdeveloped or technically unstable for development until after the first generation of HPV vaccines had been approved. Moreover, NCI scientists and clinicians had consistently reported attention to the social aims of their research, first in relation to translation and, later, global disease reduction. This evidence suggests that the NCI scientists responsible for the basic research that developed the vaccine did *not* ignore efficiency for the sake of efficacy. In fact, they actively strove to *balance* efficacy with efficiency since 1996, when human trials for the vaccine were first planned (Schiller and Lowy 1996). As Douglas Lowy, the NCI scientist who held the patent for the LI VLPs, remarked:

> [vaccine alternatives suggested from NCI-sponsored Phase II/III trials were] something that was predicted, but something that neither of the companies' trials really looked at, in part because I imagine they were really interested in trying to look at efficacy rather than effectiveness because they could sell more vaccine

> probably if they showed very high efficacy. But we were also interested in seeing what happens with overall effectiveness.[2]

As NCI scientists *did exactly what Intemann and Melo-Martín said they should do after all* without changing the outcome of vaccine R&D, the authors' counterfactual explanation fails in the face of historical analysis that includes the Institute as a major player in HPV vaccine R&D.

While Intemann and Melo-Martín are correct in principle—that social and epistemic aims are only artificially parsed, and that HPV vaccine research shows how the latter influences the former—they err in their assessment of HPV vaccine R&D by arguing for the primacy of profit motive *post hoc, ergo propter hoc*. The authors treat publications by NCI researchers involved in HPV vaccine R&D efforts as separate from vaccine development and testing, which they presume to have been controlled by Merck and GSK. Their assertion that profit motive oriented researchers toward efficacy rather than efficiency rests upon this assumption. However, the work of publicly-sponsored research at NCI was instrumental in shaping the first generation of HPV vaccines. This research yielded the very L1 VLP technology the authors critique.

The NCI's role in vaccine research and clinical testing shows the importance government research played in determining the design of first-generation vaccines. It is difficult to argue that these scientists were motivated by concerns for profit, as federal technology transfer policy capped all NIH employees' royalties at $100,000 annually at the time they patented their technology.[3] In addition to cross-licensing their patent to foster market competition and drive down prices, NCI clinicians and scientists continued their involvement in clinical testing based on their assumption that only a government Institute unconcerned with profit had the ability to

[2] Oral history interview with Douglas Lowy. February 23, 2017. Bethesda, MD.
[3] September 1, 1994 memo from NIH Legal Advisor to Robert H. Purcell, NIAID. "The $100,000 cap on royalties to inventors in the Federal Technology Transfer Act." Harold Varmus papers, Box 7, Folder 1. National Library of Medicine, Bethesda, MD.

collect more complete data on the vaccine. NCI-sponsored clinical trial protocols did not depart substantially from those of industry, except for their efforts to recruit more diverse subjects for clinical trials. Additionally, cheaper vaccine alternatives were not considered viable until first-generation HPV vaccines were in Phase III human trials. Once viable, the NCI pursued these second-generation vaccines under the impetus of reducing the global burden of cervical cancer.

HPV RESEARCH AT NCI, 1991-2008

The technology that enabled the development of the first generation of HPV vaccines originated from the work of Douglas Lowy, M.D. and John Schiller, Ph.D. of the NCI Laboratory of Cellular Oncology. Under Lowy's advisement, Schiller began investigating the papillomavirus (PV) family as a postdoctoral researcher in 1983. They aimed to contribute to the growing body of evidence that indicated infection with certain HPV strains was a necessary cause of many cervical cancers (see Aviles 2015). Schiller notes that when he and Lowy initiated their inquiry into PVs, the idea of a vaccine was far from their minds. A few researchers had previously attempted to develop PV vaccines in animal models, but these attempts had proven "miserable failures."[4] These earlier attempts used denatured PV proteins to elicit immune responses in hosts, but epitopes against PVs are conformation dependent. This means that, in order for the immune system to respond to a PV infection, PV proteins need to be properly folded. Any effective PV vaccine would thus have to introduce structurally complete PV proteins, but any safe vaccine would have to do this in a way that did not risk active infection.

[4] Oral history interview with John Schiller. April 22, 2015. Bethesda, MD.

In 1991, the NCI was cultivating a culture conducive to translational research under the guidance of Director Samuel Broder. At the same time, Schiller and Lowy made an important breakthrough that would enable development of a safe and efficacious PV vaccine that could be translated into a public health strategy to prevent cervical cancer. Schiller and Lowy successfully expressed properly self-folding L1 VLPs of bovine papillomavirus as well as HPV-16, the HPV strain most strongly associated with human anogenital cancers. They found the VLPs they produced were structurally identical to L1 proteins found on complete PVs and elicited a substantial immune response in host cells.[5]

Schiller and Lowy interpreted their findings as indicating an important breakthrough in HPV-cancer research: L1 VLPs were highly immunogenic and, because they could be manufactured apart from the nonstructural viral proteins (E6 and E7) that induced cellular transformation, could be used to develop safe and effective subunit vaccines against HPV-16 associated cervical cancer (Kirnbauer et al. 1992). Subunit vaccines delivered only small portions of a microbe into the body in order to elicit immune response, unlike the older and more common vaccine technologies that utilized live, attenuated, or inactivated microbes. The hepatitis B vaccine, which was developed to prevent liver cancers associated with the virus, was the first subunit vaccine developed using VLPs. Schiller and Lowy used the hepatitis B vaccine as a model for VLP-based HPV vaccine technologies.[6]

A strong exemplar for vaccine development was particularly important to Schiller and Lowy, as neither researcher had any prior experience in immunology or vaccinology. As Schiller recalls, they initially approached the problem of PV VLPs from a perspective oriented toward

[5] National Cancer Institute. 1992. *Division of Cancer Biology, Diagnosis and Centers Annual Report*, pg. 215. Archive.org.
[6] Interview with John Schiller.

learning about the "basic biology" of virally-induced neoplasia.[7] Schiller saw their work as developing enabling technologies for both basic and translational research efforts, and perceived such projects that "straddled the fence" between basic and translational research as ideal.[8]

The promise of translational applications for findings like Schiller and Lowy's was not lost on NCI administrators, advisors, and patrons. In September 1992, Congress singled out the development of an HPV vaccine as a particularly high priority for the Institute.[9] Intramural researchers at NCI also presented evidence that strongly suggested the potential to develop effective HPV vaccines to the National Cancer Advisory Board (NCAB), the body that granted final peer review on the NCI's extramural research program and had a strong hand in guiding priority-setting in the NCI.[10] By 1993, NCI leadership was touting the Institute's HPV research as a "significant initiative" in their long-term planning strategies.[11]

Early findings from Schiller and Lowy's lab stoked their optimism about vaccine development. As Schiller recalls, their first attempts to inoculate rabbit models against PV, begun in 1992, returned astonishing results. In these experiments, the lab produced sera that contained self-assembled L1 VLPs expressed through insect cells. Over the course of nine months, Schiller and his postdoctoral fellow Reinhard Kirnbauer injected the sera at different doses and tested the blood of infected rabbits for neutralizing antibodies. The first injection, which was diluted 1,000-fold, showed extremely high titers of neutralizing antibodies. Kirnbauer

[7] Ibid.
[8] Ibid.
[9] Text of Senate Bill, in "Senate bill matches $2.01 billion Bush request for NCI, sets bypass funding for breast cancer." *The Cancer Letter*, September 18, 1992, pg. 5
[10] December 14-15, 1992 Meeting minutes of the National Cancer Advisory Board (NCAB), pg. 29-34. NCI Division of Extramural Activities digital archive (henceforth "NCI DEA digital archive"); May 4-5, 1993 Meeting minutes of the NCAB, pg. 25-29. NCI DEA digital archive.
[11] National Cancer Institute, *Fact Book 1993*, pg. 2. NCI digital archives.

ran two more tests, one at a 10,000-fold dilution and the next at a 100,000-fold dilution. To their surprise, even the latter dose proved highly immunogenic.[12]

Schiller and Lowy were quick to act on their optimism. In 1993, after patenting their L1 VLP technology, they began soliciting every large pharmaceutical company and manufacturing firm they could to license their patent for development. Yet the pharmaceutical industry's enthusiasm for an HPV vaccine failed to match theirs: Schiller recalls being confronted by a general skepticism that a vaccine for any sexually transmitted infection could succeed. Even in the face of consistent and unequivocal evidence of immunogenicity, most pharmaceutical companies were convinced that vaccines for sexually transmitted infections would ultimately fail in the face of repeated exposures to pathogens.

Schiller and Lowy's luck changed when Merck decided to take a "leap of faith" on the vaccine.[13] Schiller credits a meeting with Maurice Hilleman, the famed vaccinologist whose credits include development of the hepatitis B vaccine, with Merck's decision to license the patent. Schiller and Lowy presented their results to Hilleman, who was still operating as an emeritus researcher at Merck. Hilleman interpreted Lowy and Schiller's results through his successful hepatitis B efforts and decided, "this is gonna work and Merck's gonna do it."[14] The next day, Hilleman persuaded Merck to contact the NCI's legal team to license Schiller and Lowy's technology.

The NCI's policy for patent licensure included a stipulation that patents be licensed to multiple entities in order to maintain non-exclusive use of intellectual property produced using

[12] Interview with John Schiller; Interview with Doug Lowy.
[13] Ibid.
[14] Ibid.

taxpayer funding. This policy was particularly important in 1993, when the National Institutes of Health (NIH) came under scrutiny over the high prices of drugs like AZT and Taxol that were developed from enabling technologies invented at the NCI. Congress criticized the NIH's inability to reign in drug prices as reflecting the Institutes' unwillingness to protect public investments in biomedical R&D. NIH Director Bernadine Healy defended the Institutes' approach to technology transfer, arguing that competitive co-licensing agreements were one of the most effective strategies the NIH could use to keep drug prices low while ensuring discoveries were translated into medical interventions.[15] In light of concerns that the NCI had "given away" the publicly funded discovery of Taxol by licensing it solely to Bristol-Myers (Goodman and Walsh 2001:160), it was particularly urgent that new drug development at NCI adhere to competitive cross-licensing practices.

Schiller and Lowy's earliest efforts to develop the HPV vaccine took place during these debates over the relationship between government basic research and private drug development. In order to maintain non-exclusivity in licensing patents and to ensure market competition, the NCI cross-licensed the L1 VLP patent to a local biotechnology firm, MedImmune. MedImmune continued animal trials around each of these technologies, and by 1997 had initiated human trials testing one of their HPV vaccine variants.[16] (Merck also began its clinical trials in 1997.[17])

[15] Statement by Bernadine Healy, Director, National Institutes of Health, Department of Health and Human Services. Senate Select Committee on Aging. February 24, 1993. NCI Office of Government and Congressional Relations, Policy Files 1980-1999 (NARA II, Record Group 443, UD-10W Entry 9, Box 1, Folder 9).
[16] "MedImmune Begins Clinical Trial With The First Preventative Human Papillomavirus Vaccine Candidate." *PR Newswire*, February 3, 1997.
[17] June 8, 2006. Letter from Nancy B. Miller, M.D., Center for Biologics Evaluation and Research, US Food and Drug Administration. "Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine (S. cerevisiae) (STN 125126 GARDASIL), manufactured by Merck, Inc." pg. 19. FDA digital archive.

In addition to the privately-funded Merck and MedImmune trials, Schiller and Lowy initiated government-funded trials to test the vaccine technology they developed. Because Lowy held the initial Investigational New Drug (IND) license for the L1 VLP technology, they were able to conduct trials on the vaccine in parallel with industry.[18] According to Schiller, he and Lowy were concerned that either Merck or MedImmune could make business-related decisions to discontinue clinical trials for any number of reasons the inventors had no control over. Furthermore, Schiller believed an NCI-funded trial had the potential to "collect a richer base of specimens and understand things" better than drug company trials, which he believed were unlikely to explore interesting data tangential to the goals of quickly developing a marketable vaccine.[19] Schiller believed that information gleaned from the clinical application of his laboratory's findings could inform further basic research.

Yet Schiller and Lowy's absence of formal training in either vaccinology or clinical trial design, and the NCI's lack of experience in producing biologicals, created barriers that necessitated collaboration outside of their laboratory. Schiller and Lowy consulted NCI epidemiologist Allan Hildesheim and Brian Murphy, an experienced vaccinologist at the National Institutes for Allergies and Infectious Diseases (NIAID). The NCI/NIAID team contracted with local biotechnology firm Novavax to develop the L1 VLP vaccine in sufficient quantities for a small-scale Phase I human trial. They then teamed up with the Center for Immunization Research at The Johns Hopkins University, which specialized in conducting human vaccine trials. The Johns Hopkins team designed the protocols and recruited subjects, while Schiller and Lowy integrated epidemiological and clinical trial findings into their

[18] Interview with Doug Lowy.
[19] Interview with John Schiller.

understandings of how HPV could be studied in their laboratory. This multidimensional approach to collaboration at NCI was at the same time innovative in its ability to unite academia, industry, and government science in short-term voluntarist collaborations and consonant with the approach to translational research NCI administrators hoped to foster.

By 1996, Phase I findings suggested the vaccine would be safe enough to test on a larger human population. Around this time, Schiller and Lowy initiated a series of collaborations with Mark Schiffman, an intramural NCI epidemiologist at the newly-restructured Division for Cancer Epidemiology and Genetics. Schiffman was Principal Investigator on a study launched in 1993 that aimed to track the natural history of HPV infection in women in Guanacaste, Costa Rica over 7 years. Schiller and Lowy convinced Schiffman to collaborate on modified arms of the Guanacaste trial that would test an assay for HPV antibodies they had developed, and, beginning in 1997, would serve as Phase II and III trials for their L1 VLP vaccine.[20]

Then-NCI Director, Richard Klausner, proved an early supporter of HPV vaccine efforts. Like Broder before him, Klausner treated vaccine-oriented research on HPV as one of the Institute's most significant translational undertakings. In September of 1996, less than a year after his appointment, Klausner convened an internal NCI meeting to discuss the Institute's role in promoting HPV vaccine development.[21] Klausner was particularly keen on the collaboration Schiller and Lowy were developing with Schiffman, and he held up HPV vaccine efforts as exemplary of the kind of cross-divisional interactions he hoped his organizational reforms would encourage.[22]

[20] Director, National Cancer Institute. 1997. *The Nation's Investment in Cancer Research: A Budget Proposal for Fiscal Year 1999*, Pg. 9. Government Printing Office digital archives (henceforth GPO digital archives).
[21] September 10-11, 1996, Meeting minutes of the NCAB, pg. 9. NCI DEA digital archive.
[22] November 19-20, 1996, Meeting minutes of the NCAB, pg. 10. NCI DEA digital archive.

Despite Klausner's formal support of the project, the NCI lacked a clear trajectory for translating laboratory findings into vaccines. Klausner's enthusiasm for the HPV vaccine effort did not reflect the Institute's dominant focus when it came to translational research. Instead, NCI leadership was banking on the potential of genomic information to yield new approaches to diagnostics and treatment.[23] As such, Lowy and Schiller depended upon their colleagues at NIAID to guide them through the process of interacting with the FDA to set up human trials.[24]

When it came to executing the trials in Guanacaste, Lowy and Schiller's relationship with Schiffman and Hildesheim were also essential to their success. As Schiller recalls, these relationships "developed very naturally" in the NCI.[25] Though neither Schiller nor Lowy had worked with epidemiologists prior to their HPV vaccine efforts, they were familiar with Schiffman and Hildesheim from joint meetings with their division in the NCI's extension at Shady Grove, Maryland. When the time came, they found that such collaborations were encouraged in the Institute. In turn, NCI leadership would invoke joint projects between Schiller and Lowy's lab and Schiffman and Hildesheim as examples of successful collaboration encouraged by the organizational culture of the NCI.[26] In comparison to the Phase I Johns Hopkins trial, the Guanacaste trials illustrate how Klausner's reforms created the means for collaborating to test drugs in-house more easily than in previous years. These reforms, which were done to increase the "intellectual infrastructure" for translating research[27], incentivized Schiller and Lowy to shift their vaccine efforts inward.

[23] Director, National Cancer Institute. 1996. *The Nation's Investment in Cancer Research: A Budget Proposal for Fiscal Years 1997/1998*. GPO digital archives.
[24] Interview with Douglas Lowy.
[25] Interview with John Schiller.
[26] December 4-5 2002 Meeting minutes of the NCAB, pg. 33-34. NCI DEA digital archive.
[27] September 12-13, 1995 Meeting minutes of the NCAB, pg. 11. NCI DEA digital archive.

Though Schiller and Lowy could now collaborate with other NCI scientists to test their vaccine technology in human trials, they still relied upon collaborations with private entities to develop the vaccine to scale. Following promising Phase I results, MedImmune transferred its license for their L1 VLP technology to GlaxoSmithKline, who were developing Cervarix as a competitor to Merck's Gardasil.[28] Schiller and Lowy chose to use GSK's formulation, as the pharmaceutical giant could provide sufficient material to meet their goal of vaccinating up to half of the Guanacaste study cohort of 10,000 women. As Lowy reported, GSK was happy to oblige.[29] Schiller announced the 3-4 year Phase II/III Guanacaste trials to the NCAB in 1998, just as the Phase I trials at Johns Hopkins were wrapping up.[30]

For years, collaborative efforts for HPV vaccine development in the NCI had been receiving praise for their attention to clinical trial diversity. As Schiller noted in a 1998 NCAB meeting, the Phase I trial at Johns Hopkins included "strong representation" of African-American women, and the Phase II/III Guanacaste trials not only enrolled a predominantly Hispanic population, but women whose circumstances more closely resembled those of the majority poor women who would die from HPV-related cervical cancer.[31] Cervical cancer disparities, which are particularly striking among African-Americans and Hispanics, were singled out as the first target for the NCI's newly-founded Center to Reduce Cancer Health Disparities in 2001. There was a sense among NCI researchers that cervical cancer was a

[28] Interview with John Schiller.
[29] Interview with Doug Lowy.
[30] December 9-10 1998 Meeting minutes of the NCAB, pg. 15. NCI DEA digital archive.
[31] Ibid.

problem "we have an answer to," and that disparities among underserved populations were even more striking in the face of imminent cure.[32]

By 2001, discussions of HPV vaccine research in the NCI's strategic planning process were permeated by the language of health disparities. In the Bypass Budget, the NCI directorate's major annual strategic planning document, the HPV vaccine was promoted as the best strategy for "comprehensively controlling" HPV infection and consequently eliminating health disparities in cervical cancer morbidity and mortality in the US and abroad.[33] Similarly, the NCI-sponsored Gynecological Cancer Progress Review Group Report released in 2001 listed HPV vaccine development as one of the two highest priorities in the field, due to its "high-impact" capacity to virtually eliminate cervical cancer worldwide.[34] For NCI strategic planning purposes, the HPV vaccine promised a technical solution that would deliver real reductions in health disparities, both among racial and ethnic minorities and Whites in the US and among developing nations and the developed world.

Given Lowy's prominent role in strategic planning and his continued ascent through the NCI's administrative apparatus, this shift in the language of strategic planning was likely influenced directly by the NCI's intramural vaccine development program. It had certainly been prefigured in the work of the NCI laboratory scientists and their epidemiological collaborators for at least five years prior. As Schiller and Lowy first noted in a 1996 publication, the majority of women who died of cervical cancer lived in developing nations. While lack of infrastructure

[32] "NCI Health Disparities Center describes 'think tank' projects for policy change." *The Cancer Letter,* April 27, 2001, pg. 2.
[33] Director, National Cancer Institute. 2001. *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2003*, Pg. 49. GPO digital archives.
[34] National Cancer Institute, "Report of the Gynecological Cancer Progress Review Group," November 2001, pg. 7. NCI digital archives.

made delivery of the vaccines being developed based on the hepatitis B model difficult to implement in these settings, Schiller and Lowy maintained that "an effective HPV vaccine may have a greater potential for reducing worldwide cancer burden than any other currently conceived anticancer program" such as routine Pap screening (Schiller and Lowy 1996:373). Schiffman and Hildesheim shared this opinion (Sherman et al. 1998). The solution to barriers against vaccination with a L1 VLP vaccine, according to these NCI scientists, was to explore alternative vaccine models more appropriate for resource-poor regions, including naked DNA vaccines, recombinant vaccines using live bacterial vectors, or transgenic plants that would allow VLPs to be ingested as food. However, as Schiller and Lowy noted, none of these different strategies was very well developed. While they continued to discuss these approaches as alternatives better suited for developing nations for another 10 years, they consistently cautioned that these technologies had not been demonstrated to be safe or efficacious (Schiller and Nardelli-Haeflinger 2006). Some of them, such as naked DNA vaccines, Schiller admitted to having little faith in as early as 1998.[35]

Yet the NCI had created opportunities to sponsor these alternatives, which at the time were not at an appropriate stage for development. They funded efforts to develop second-generation vaccine alternatives that NCI administrators saw as extending or complementing ongoing work in the intramural program.[36] These projects included grants awarded to academic collaborations with biotechnology firms exploring second-generation prophylactic HPV vaccines that promised to be "both economical and stable."[37] However, it is worth noting that these

[35] December 9-10 1998 Meeting minutes of the NCAB, pg. 15. NCI DEA digital archive.
[36] Director, National Cancer Institute. 2001. *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2003*, Pg. 82. GPO digital archives.
[37] Director, National Cancer Institute. 2003. *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2005*, Pg. 27. GPO digital archives.

alternatives had not reached a stage of development where they could be considered viable until 2003. Even a 26% increase in the NCI's investments in novel HPV vaccine research between 2002 and 2003[38] left these alternative efforts at a major disadvantage vis-à-vis first-generation vaccines: by this time, NCI and industry Phase III human trials on the first-generation L1 VLP vaccine were well underway.

The results of these human trials, much like animal trials before them, were initially very promising. By 2002, data from the NCI Phase II study, along with the private Merck and GSK trials, began trickling forth in talks and publications.[39] Congress broadly supported these efforts, encouraging continued and accelerated collaboration within the NCI as well as with industry toward the end of manufacturing an effective prophylactic vaccine.[40] The NCI also provided a substantially more encouraging environment for collaborations with industry. Alongside HPV vaccine efforts, the NCI had been ramping up other project-based collaborations between federal agencies and industry. A good example of these efforts included the Cancer Genome Anatomy Project, which comprised partnerships between scientists in the NCI, other NIH laboratories, the Department of Energy, and private firms GlaxoSmithKline, Merck, Genentech, and Bristol-Myers Squibb.[41] However, where these larger-scale genomics projects once again suffered under the weight of disappointment that the Human Genome Project had not yielded immediate tools for intervening in human cancers, the HPV vaccine provided a likely win for translational research at NCI.

[38] National Cancer Institute, *Division of Extramural Activities Annual Report 2003*, pg. 157. NCI digital archives.
[39] December 4-5 2002 Meeting minutes of the NCAB, pg. 33-37. NCI DEA digital archive. Also see Koutsky et al. 2002.
[40] Senate Appropriations Committee Report in "Senate calls cancer research a priority, cites research task force funding goal." *The Cancer Letter*, October 8, 1999 pg. 5, 7; Senate Appropriations Committee Report in "Senate approves 15% increase for NIH; House passes 5.6% raise, but favors more." *The Cancer Letter*, July 7, 2000, pg. 4
[41] February 25-26 1997 Meeting minutes of the NCAB, pg. 7. NCI DEA digital archive.

Between 2002 and 2006, industry clinical trials ran simultaneously with trials sponsored by the NCI. Merck's trials, which enrolled over 25,000 subjects, concluded in late 2005. The FDA approved Merck's Gardasil in June 2006.[42] GSK's Phase III trials for Cervarix, which enrolled 30,000 women, concluded in 2006.[43] Cervarix was approved for use in Europe in March 2006, but stalled in the FDA until 2009.

NCI scientists saw special value in conducting parallel efficacy trials whose protocols were designed and controlled by the Institute. Throughout the Phase II and III Guanacaste trials, the NCI team continued to track women who had violated the three-shot protocol rather than dropping them from the study, as they assumed drug companies would do (in this case, Merck continued to follow protocol violators in at least one trial).[44] Schiller argued that only government trials could afford to follow protocol violators because they were not motivated by profit.[45] Though not completely true in this instance, such beliefs about the NCI's role as a supplementary force in R&D were important motivators for conducting follow-ups. These follow-ups showed that even women who failed to complete more than the first shot in the three-shot protocol showed antibody titers sufficient to suggest protection against the targeted HPV strains up to seven years after administration. These findings have led Schiller and Lowy to advocate for further research on a one-shot protocol for the first-generation vaccine as the most viable alternative for vaccinating women in developing countries.[46]

[42] June 8, 2006 Letter from Nancy B. Miller; "Vaccine prevented cervical pre-cancers, non-invasive cancers in Phase III trial." *Clinical Cancer Letter*, October 2005, pg. 2.
[43] "Cervical cancer vaccine more active in teen girls." *Clinical Cancer Letter*, February 2006, pg. 5.
[44] In this case, Merck followed one small group of women who violated protocols for two years, and found that a single dose of the vaccine was 97% effective at preventing cervical cancer surrogate endpoints. See "Vaccine prevented cervical pre-cancers, non-invasive cancers in Phase III trial." *Clinical Cancer Letter*, October 2005, pg. 2.
[45] Interview with John Schiller.
[46] Ibid.; Interview with Doug Lowy.

In the interim, Schiller's skepticism of industry's commitment to vaccine alternatives led him to pursue collaborations in India. Schiller encouraged utilizing manufacturers in Latin America and Asia as a solution to patent restrictions (resulting from an agreement between Merck and GSK to cross-license their vaccines[47]) that hindered exploring generics and vaccines in North America and Europe (Schiller and Nardelli-Haefliger 2006:S152). The NCI's quest for cheaper generics once again placed the Institute in a supplementary position in vaccine R&D. Initially, Schiller was optimistic developing nation pharmaceutical manufacturers could produce generics of the first-generation HPV vaccine at greatly reduced cost. Schiller's optimism for this project was fueled in part by the success of Indian manufacturers to slash the cost of hepatitis B vaccine generics from Merck's price of over $300 to only 30 cents per dose.[48]

As it turned out, Indian companies were reluctant to pursue development of generics when the status of intellectual property rights around HPV vaccines was ambiguous given the recent enactment of the World Trade Organization's Trade-Related Intellectual Property Rights (TRIPS) in India (Padmanabhan et al. 2010:675-6). Their hesitation reflected a historical moment where a legal battle over Novartis's right to enforce their patent for Glivec in India held the future of India's intellectual property policies in suspense (Ecks 2008). As Lowy explained, the agreement NIH made when co-licensing their technology to Merck and GSK contained a specific provision that allowed companies outside the protected markets of North America and Europe to immediately develop generics for low-income countries.[49] Indian industry's

[47] Candace Hoffmann. "Merck & Co., GlaxoSmithKline sign cross-licensing agreement for HPV vaccine." *FirstWorld Pharma*, February 3, 2005.
[48] December 6-7 2005 Meeting minutes of the NCAB, pg. 38. NCI DEA digital archive.
[49] Interview with Douglas Lowy.

skittishness over developing generics was unfounded but nevertheless consequential, as it prevented Schiller from finding a company to partner with to produce generics.

Dissuaded from pursuing generics, Schiller and his colleagues forged a number of collaborations with Indian biotechnology and pharmaceutical companies in an effort to extend access to HPV vaccines to developing nations through the production of more effective second-generation vaccines. In 2007, Schiller collaborated with Shantha Biotechnics in the hopes of bringing a second-generation vaccine based on patent-pending L2 VLP technology to market at an initial cost of $15 per dose (Padmanabhan et al. 2010:673). They hoped to reduce this price to $1-2 per dose in the ensuing years to make it more feasible for global distribution (Padmanabhan et al. 2010:674).

By the time Gardasil was approved by the FDA in 2006, it had also become clear to administrators in the NCI, like then-Director John Niederhuber, that the purpose of continued vaccine development efforts was to extend coverage to underserved populations throughout the globe.[50] The vaccine was quickly held up by NCI advisers as a "true example of translational research."[51] Testifying before Congress in 2006, Niederhuber insisted that the HPV vaccine could make a huge impact on cancer rates in the middle- and low-income countries that bear the greatest burden of HPV disease.[52] For NCI leadership, the story of HPV R&D illustrated 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

[50] See, for example, Niederhuber's testimony before the Board of Scientific Advisors on June 29, 2006, which substantially echoes the testimony Schiller gave before NCAB in December 2005. June 29-30 2006 Meeting minutes of the Board of Scientific Advisors, pg. 7 NCI DEA digital archive.
[51] November 27 2007 Meeting minutes of the NCAB, pg. 12. NCI DEA digital archive.
[52] "Remarks on HPV vaccines, SPORE funds create controversy for NCI's Niederhuber." *The Cancer Letter*, April 14 2006, pg. 4-5.

problems, and in this case, perhaps the elimination of cervical cancer as a threat to women's health."[53]

DISCUSSION: THE NCI'S CONTINUED ROLE IN HPV VACCINE DEVELOPMENT

Attention to NCI scientists' and administrators' situated and evolving understandings of translational research helps us understand why explanations like Intemann and Melo-Martín's overstate the role of pharmaceutical companies in decision-making around HPV vaccine R&D. By including NCI studies in the parameters of HPV vaccine trials, we see that the Institute did attempt to pursue multiple strategies that were informed by an understanding of their role in eliminating global cervical cancer disparities. We also answer the question begged by Intemann and Melo-Martín: "the question of which social values and aims should be endorsed and who, exactly, should be making such decisions" (2010:211). The licensing agreement Merck and GSK came to with the NCI allowing simultaneous development of generics for low-income markets put them in implicit agreement with the Institute's social aims, and positioned the NCI as a countervailing force concerned with ensuring the technology they developed best served the public good.

The NCI's goals to address global health needs benefited in that pharmaceutical companies possess double bottom-lines—i.e. they are oriented toward generating both economic and social value (see Barman 2016). The role Western pharmaceutical companies play in "gift" regimes, whereby they make large donations of vaccines and drugs to NGOs that distribute them to low- and middle-income countries, creates multiple standards of valuation for their products

[53] Director, National Cancer Institute. 2006. *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2008*, Pg. 7. GPO digital archives.

(Ecks 2008; Sunder Rajan 2006). While Merck profited handsomely from Gardasil sales in patent-protected markets, the company also donated millions of doses to low-income countries through a charitable partnership with PATH called the GARDASIL Access Program (Merck 2017). When it comes to competing generics for Gardasil, Merck has formally expressed that "Low-cost HPV vaccines targeted at 53 low-income countries… wouldn't impact the company's income as it has already committed to no-profit pricing for Gardasil in those nations" (Gokhale 2015). Merck has even partnered with the Instituto Butantan in Brazil to produce Gardasil generics at the cost of approximately $10 USD per shot (Department of STD, AIDS and Viral Hepatitis 2014). Rather than assume that profit motive guided development of HPV vaccines at Merck, one could ask which of the competing orders of valuation—economic or social—prevailed in decision-making at the company during different stages of development. This is an empirical question that is unfortunately beyond the scope of this study. However, noting Merck's organizational incentive to generate social value further troubles Intemann and Melo-Martín's assumption that profit motive explains the shape of their vaccine technology.

If NCI scientists are correct, the potential to develop more ethical vaccine technologies may lie with Indian biotechnology and pharmaceutical companies. The Indian government has framed its support of private biotechnology and pharmaceutical enterprises in the context of achieving public good. India's Ministry of Science and Technology mandates that for-profit entities that depend upon India for research or development reinvest a percentage of their annual profit into the community (Rajan 2006:69). To be sure, as Stefan Ecks (2008) has pointed out, Indian industry has moved closer to Western market approaches since it joined the World Trade Organization in 1995. Sunder Rajan demonstrates how such "harmonization" with the WTO preserves the global hegemony of Western pharmaceutical companies (Sunder Rajan 2017).

Nevertheless, economic incentives for start-ups and intellectual property regimes that continue to defy Western efforts to extract profit from developing markets have maintained a distinct political economy of R&D in India attractive to NCI actors whose work aims to rectify global health inequalities.

At the time of this writing, none of Schiller and his colleagues' collaborations with Indian companies for second-generation HPV vaccine development have yielded substances ready for market. The Shantha partnership met its demise in 2014 after technical problems with developing an L2 VLP vaccine were deemed too complicated to proceed further (Kaur Batra 2014). Schiller's former colleague Nardelli-Haefliger's collaboration with Indian Immunologicals to develop a second-generation L1 vaccine using live bacterial vectors, initiated 10 years prior, is still ongoing (Schiller and Müller 2015). Historically, concerns over infrastructure, technical capacity, and quality control for vaccines manufactured in the global South have plagued similar efforts to innovate alternative technologies for hepatitis B and other common childhood vaccines (Muraskin 1995; Muraskin 1998). It thus remains to be seen whether the NCI can successfully collaborate with private organizations that prioritize the public good over profit more effectively than their first-world counterparts.

CONCLUSION: AN EMERGENT ETHICS OF HPV VACCINE DEVELOPMENT AT NCI

Whatever the outcome of Lowy and Schiller's ongoing efforts, this case study demonstrates that NCI researchers cannot be imagined to sit outside of the development process of HPV vaccines as they proceeded in industry. NCI researchers were part and parcel of the vaccine's development, pushed for stipulations in their licensing agreements with Merck and

GSK that ensured generics could be simultaneously developed for low-income countries, and independently tested the same compounds in human trials at the same time industry conducted private research. Additionally, Schiller and Lowy actively pursued alternative vaccine strategies based on an evolving understanding of HPV vaccine R&D as a translational initiative that could eliminate health disparities in the US and around the globe. In other words, these NCI researchers were motivated by the aims of efficacy *and* efficiency throughout the initial development and subsequent clinical testing of first-generation HPV vaccines. That the NCI did not produce vaccine alternatives in time to challenge the first-generation models they helped industry develop does not reflect a lack of vision for global health disparities. Instead, it reflects conjunctures of technical, organizational, and institutional environments that made it implausible such alternatives would be developed along the same time horizon as first-generation vaccines, regardless of how seriously NCI researchers took the social aims of global disease reduction.

This analysis of the role organizational cultures of translational research played in shaping HPV vaccine R&D at different moments in time suggests that the relationship between social and epistemic aims are not only multiple, but also emergent from local environments. It further suggests that STS scholars should ground their explanations in interpretations of the most plausible alternatives actors could choose from in light of their temporally and spatially situated practical activities, rather than analysts' understandings of how transcendent values shape possible worlds. In understanding how NCI scientists developed goals related to reducing health disparities through HPV vaccines, we can come to understand more concretely the possibilities for ethical action as they inhere in lived historical events.

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