

Summary

Adenovirus-Based Oncolytic Therapy: An Exploration of Dynamics Within Its Development

In this paper, I explored the case of oncolytic adenoviruses, which are essentially common cold viruses engineered to specifically target and kill cancer cells. As a lab researcher, I explain the mechanisms and logic on which this therapy is based. The research behind this treatment was first established in academic and government-affiliated laboratories, then industry took over developing the viruses. Despite excitement and anticipation surrounding this virus in the late 1990s, only China has so far approved its clinical use.

This situation was shaped by many forces. There was the highly publicized death of a healthy teenager in an adenovirus-mediated gene therapy trial that shook and slowed down the field. Although oncolytic therapy is technically not gene therapy, it also utilizes adenoviruses and was similarly touted as a magic bullet—hence the field was impacted negatively. Results from clinical trials using ONYX-015 also did not live up to the hype, though they were promising nonetheless.

At the same time, the same exact virus was being developed by Sunway Biotech in China. By copying ONYX-015, China was able to skip through the requisite early steps of basic research, and the government itself offered plenty of support. The poorer health infrastructure also enabled researchers to quickly gather participants for clinical trials, which demonstrated very favorable benefits caused by the virus (renamed H101). Differences in clinical trial regulations between China and US contributed to these improved results in Chinese trials.

Yet throughout all this, certain facets of cancer remain missing from the discussion. These include the bigger picture topics of prevention, prevalence, etc. Forces are at work that encourage the narrow scopes commonly held by scientists, reducing human beings down to cells. Accordingly, humanistic data are missing as well, mostly due to ethical considerations—such information would help humanize the treatment.

In terms of future research, I suggest taking advantage of the situation in China to address questions such as the effectiveness of the therapy, people's reactions to it, plus how to increase its accessibility. China is therefore a convenient surrogate for a postmarketing surveillance of oncolytic therapy. Data gathered here will guide the future of the field in the United States, whether a resurgence should be encouraged or whether focus should be shifted elsewhere.

**Adenovirus-Based Oncolytic Therapy:
An Exploration of Dynamics Within Its Development**

By Janie Qi

When I first joined Dr. Jane Flint's lab, I was given a tour throughout the laboratory space. Aside from the usual lab benches and piles of reagents, familiar sights in any lab, I was also introduced to two special rooms: a tissue culture room and a virus room. In the tissue culture room, things are kept as sterile as possible—here is where we grow human cell lines, whether they be cervical tumor cells, kidney cells, etc. Adenoviruses, on which the lab's research is carried out, are confined in the virus room: we bring human cells in here and carry out infections in a sterile, controlled environment.

Whereas I was informed that the separation of viruses into a single room is meant for the safety of individuals working in the lab, I could not help but remember Latour's discourse on the laboratory's power. Namely, a laboratory is able to destabilize the relationship between pathogens and infected animals (Latour, 1999). Moreover, the adenoviruses from which we must shield ourselves with protective gear look anything but threatening—they are microscopic in scale, after all—in transparent liquids contained in little Eppendorf tubes. The only time we “see” them is through their killing trails, as little circles visible on a plate known as plaques, which are clusters of cells infected and lysed by a virus. Anytime we are done with whatever purpose we have for a batch of adenoviruses, we easily kill them with household bleach. Against us scientists, they are powerless, and we fully tame them for our goals.

It is therefore easy for me to forget that these viruses we work with are something of a big deal, so to speak. The adenoviruses in our lab are capable of specifically targeting tumor cells and killing them, providing the basis for what is called oncolytic therapy. As for exactly how the viruses go about doing that, the underlying principles are not overly complicated.

Basically, cancer cells are intrinsically different from non-cancerous cells in certain ways. Due to one particular characteristic of tumor cells, as well as deliberate tampering in the viral genome by scientists, this virus can only infect and kill tumor cells.

More specifically, the special characteristic in question is that a majority of cancer cells have a mutation that distorts the protein p53 (Hollstein, Sidransky, Vogelstein, & Harris, 1991). This protein has a major role in controlling cell growth in the event of DNA damage (Sherr, 1996). Without functional p53, a cell with impaired DNA, which under normal circumstances would either stop growing or undergo suicide, would instead grow uncontrollably, turning into an immortal tumor cell. As tumor cells divide and increase, they first interrupt local tissue function, then organ function, eventually spreading to other parts of the body to inflict damage elsewhere (Hanahan 2000).

In this pathway of cancer development, oncolytic adenoviruses interfere near the beginning. They have been engineered such that they can grow only in cells without functional p53 (i.e. cancer cells), and normal cells are left unharmed, the ideal sort of treatment for cancer (Yamamoto & Curiel, 2010). Imagine the excitement of researchers, health professionals and patient populations affected by cancer when, in the late 1990s, such viruses were introduced—these had the potential to serve as all-purpose cancer killers, due to the ubiquitous nature of the p53 mutation among cancers. Even better, these viruses induce only mild clinical symptoms in humans (Berk, 2007), such that their administration would be relatively safe. Yet we are now in the year 2010; over a decade has passed since oncolytic adenoviruses were developed in the United States, but so far they have been approved for cancer therapy in China, and in China only. What happened? Why have these viruses not made a bigger splash in the field of cancer

treatment? This topic will be explored in the ensuing discussion and will evoke recurrent themes in global health science.

In order to get a better understanding of the situation, it is necessary to take a few steps back into history. Adenoviruses were first isolated in 1953 by researchers looking for causes of the common cold. The backdrop for this discovery is an institutionalized quest among scientists for disease-causing microbes, which is a mindset rooted in germ theory that originated in the second half of the 19th century (Lederberg, 2000). Since then, numerous types have been identified, and a great deal of information about the virus has been uncovered. These viruses are linked to infections of the respiratory tract, with usually mild, self-limiting symptoms. Investigations into characteristics of the virus have illuminated important principles for the field of biology, most notably the mechanisms of mRNA processing, which is an integral part of genetic information being translated into functional proteins (Berk, 2007).

The viruses also became useful systems for examining the development of cancer, once they were demonstrated to be capable of turning mouse cells into cancer cells (Trentin, Yabe, & Taylor, 1962). All components of the virus, from the icosahedral capsid to core proteins, and the complex interplay of viral proteins and cellular proteins during infection, were scrutinized and characterized (Berk, 2007), as scientists usually do. Such baseline research was largely carried out in government laboratories or laboratories in academia.

Along the way, links were uncovered between specific viral proteins and tumor development. In the late 1980s, the E1B proteins were determined to be integral to an adenovirus' ability to transform a normal cell into a cancerous cell (Barker & Berk, 1987). The investigations into the direct connection between p53 and tumors, which generated huge ripples in the field, were presented around the same time in the early 90's (Hollstein, Sidransky,

Vogelstein, & Harris, 1991). Then these divergent branches of research into cancer development were brought together by scientists who demonstrated that the adenoviral protein E1B 55-kDa acts to inhibit p53 in the cell during an infection, thus playing a significant role in transforming the cell (Debbas & White, 1993). Excitement surrounding this discovery grew—in fact, Dr. Flint’s lab, with which I am affiliated, continues to focus primarily on this single protein, E1B 55-kDa.

Like the rest of adenoviral research, the monumental findings described above arose from government-affiliated or academic labs. Then just a few years later, as if a baton touch had occurred in a relay against cancer, it was the work of scientists in industry that gave rise to cancer-killing viruses. This fits well with the usual pattern of drug development, as explained by Adel Mahmoud: ideas arise in academia, then industry develop the ideas into a product (personal communication). ONYX Pharmaceuticals, a small biopharmaceutical company founded in 1992, constructed a mutated adenovirus named ONYX-015 in 1997 (Heise et al., 1997). In particular, the gene encoding the E1B 55-kDa protein was inactivated in this virus in order to target tumor cells with mutated p53. This development launched a series of clinical trials to test the efficacy and effectiveness of the virus in treating tumors, while ONYX Pharmaceuticals was awarded a US patent on the methodology utilized (Cohen & Rudin, 2001).

The reasoning behind ONYX-015’s function built on previous academic and governmental research regarding E1B 55-kDa and p53. E1B 55-kDa usually “quenches” p53 (such anthropomorphization of biological components is typical for discussions of concepts among scientists) to prevent p53 from stopping cell (and virus) growth. An adenovirus without E1B 55-kDa, like ONYX-015, cannot grow in normal cells because p53 will prevent virus activity, but in cancer cells, p53 is already “gagged”—hence ONYX-015 can specifically grow

in and kill tumor cells (Yamamoto & Curiel, 2010). The one caveat here, then, is that the virus cannot work against tumor cells where p53 remains functional, such that ONYX-015 activity depends on the p53 status of the tumor type.

This logic made sense, but scientists are always cautious about accepting new truths. After all, not only do quests for the true truth make science an intellectually attractive pursuit, they also fuel research, drawing grants and funding to support laboratories. In this case, doubts were confirmed: the replication of ONYX-015 was found to be irrelevant to the p53 status of the tumor cell line. Instead, factors like multiplicity of infection, cell type, and cell cycle phase were shown to be more accurate predictors of ONYX-015 activity (Harada & Berk, 1999; Rothmann, 1998). Such evidence chipped away at the basis of ONYX's patent as well as the logic behind ONYX-015's anti-cancer activity.

Additionally, by around the turn of the 21st century, 15 clinical trials involving approximately 250 patients had been performed regarding adenoviruses in cancer treatment. Among these, the trials that employed ONYX-015 alone yielded somewhat disappointing results. However, when administration of the viruses was combined with chemotherapy, the benefits were significantly greater and warranted further inquiry (Wildner, 2005). Yet ONYX eventually shifted priorities—after attempts to find a partner company to help pay for development of ONYX-015, no prospects emerged, and the project was dropped in 2003. Instead, more funding and efforts were dedicated to a less radical approach, in the form of a cancer drug (Pollack 2005), and not some live, cancer-fighting agent.

What prompted the rapid switch by ONYX from a rather exciting, radical focus on tumor-killing adenoviruses to a comparatively conventional focus on anti-cancer drugs? The transition evokes a rejection of viruses as a therapeutic agent to be used inside humans. This

situation brings to mind Lederberg's discussion of the prevalent attitude toward germs in general, in which he argues that people tend to antagonize them: microbes are "evil" agents that infect humans, who are "good" (Lederberg, 2000). The original idea to convert adenoviruses to "our side," so to speak, by engineering them to promote their cancer-killing functions, countered Lederberg's discourse as well as germ theory, since in this case the injected viruses were intended to cure disease instead of causing it. Therefore the decreased emphasis on adenoviral therapy reflected a sort of a reverting to the way things were before, in terms of attitudes toward pathogens.

Indeed, negative publicity surrounding a death in a gene therapy trial ignited negative attitudes toward adenovirus-based therapy (Pollack 2005). On September 17th, 1999, 18-year old Jessie Gelsinger died following administration of adenoviral vectors in a clinical trial conducted at the University of Pennsylvania (Marshall, 1999). While he was afflicted with an inherited deficiency in the enzyme ornithine-transcarbamylase (OTC) that interrupted his metabolism of ammonia, he was on the whole fit before participating in the trial; thus he was the first patient ever to die as a result of gene therapy. His death was vividly described as "the latest blow to a field that has been struggling to live up to the promise and hype surrounding the first gene therapy trials a decade ago" (Marshall, 1999).

The adenovirus used in the trial was disabled, such that the virus itself could not inflict significant damage, and carried a gene encoding OTC. It was intended to affect only the liver, not any other organs, and to transduce cells so that they incorporate and express the OTC gene. In Gelsinger's case, the actual events that occurred were almost the opposite of the predicted sequence of events. The adenoviruses did reach the liver, but they invaded numerous other organs as well. Furthermore, the ultimate purpose of inducing OTC gene expression was not

realized—with just 1% of packaged genes expressed after a whopping 38 trillion virus particles were injected, the adenoviruses were far from being able to complement the enzyme deficiency. On the other hand, the adenoviruses strongly stimulated innate immune response in Gelsinger, and these systemic inflammations resulted in his death (Marshall, 1999). Here, then, was a worst-case scenario where not only did the adenovirus injection fail to work as intended, but it actually killed the patient.

Was Gelsinger an anomaly? At a meeting held soon after Gelsinger's death, gene therapy experts generally agreed that his case was an abnormal one, yet there were opposing opinions: one expert noted that adenoviruses were known to induce immune response in host organisms, and since the Penn team continued to increase the dose, an inflammatory reaction was inevitable. It also remained unclear why intended levels of gene expression were not achieved; this was a perennial problem for gene therapy, which was generally more effective in animal trials than in trials involving human participants (Marshall, 1999).

In any case, the FDA issued a reprimand of the affiliated researchers (Stolberg, 1999a). Following Gelsinger's death, the FDA “slammed the brakes” on studies in the nation involving gene transfer via viral vectors, and suspicions of foul play during the Penn trial enhanced an image of “investigator hubris” on the part of the clinical investigators (Scott, 2008). Journalists reported that the informed consent form presented to Gelsinger omitted some information on risks, that Gelsinger was treated despite actually being ineligible for the trial due to poor liver function (Stolberg, 1999a), and that there were financial conflicts of interest (Scott, 2008). Simultaneously, patient advocacy groups called for a halt to clinical trials of similar nature, whereas industry representatives warned that the hoopla might mislead the public (Pollner, 2000). All throughout, the Penn researchers maintained that there was no wrongdoing involved

(Stolberg, 1999a). This situation illuminated the complex interplay of actors in the troubled field of gene therapy.

As for cancer-killing adenoviruses, some scientists consider the treatment a form of gene therapy (Pollack 2005), but technically no gene is delivered, which is central to the definition of gene therapy. Hence oncolytic therapy is more like a parallel field than one that's included in gene therapy. Yet injecting viruses to cure cancer appears very much similar to injecting viruses to cure a genetic disease. Thus investigations into oncolytic therapy were not shielded from the major ripples that shook the field of gene therapy, which was just 9 years old at this time (Stolberg, 1999b). Both gene therapy and oncolytic therapy had originally been touted as potential magic bullets—"rapid, quick, easy, early cures" according to W. French Anderson, the "father of gene therapy"—in the fight against inherited diseases and cancer, respectively (Pollack, 2005; Stolberg, 1999). Neither had been able to meet the hyped-up expectations that accompany any sort of magic bullet approach, such that the fall occurred just as quickly as the initial rise.

This trajectory of oncolytic therapy described here (in parallel with gene therapy) helps illustrate why ONYX-015 fell from favor in the United States. The actors and events involved can be summarized in a nutshell: in the beginning, academic and government-affiliated researchers had built up the foundations of knowledge for the virus, and then industry took over development of ONYX-015 as a therapeutic agent. Clinical trials involved clinical investigators and patient volunteers and yielded results that gave hope, albeit not as extraordinary as anticipated. Around the same time, the related field of gene therapy was destabilized by a widely publicized tragedy in a clinical trial, escalating into a closely scrutinized controversy that intimately involved clinicians, patient advocacy groups, industry, government agencies and the

media. Due to all of this, negative stigma began to envelope adenovirus-based therapy. One can easily see how deeply science in the form of cutting-edge technology is influenced by forces in society, as Lewontin had discussed (Lewontin, 1992).

In the meantime, the situation was drastically different in China. No stigma was attached to the field of gene therapy which, admittedly, was far smaller there with only 5 trials counted in late 2003 (Jia, 2006). Research on a mutated adenovirus identical to ONYX-015 was steadily under way. The resemblance was not pure coincidence, but rather the result of deliberate copying by a Chinese biotechnology company, Shanghai Sunway Biotech, without notifying ONYX (Pollack 2005). This was possible because the rights to ONYX-015 were not protected there, and similar *déjà vu* have been observed for other experimental drugs in China (Jia & Kling, 2006). In this way, China was able to take a shortcut, skipping through initial phases of academic and government research that precede industrial development, which constitute the usual pattern in the United States (Adel Mahmoud, MD, personal communication).

Renamed H101, the virus was used in clinical trials involving patients afflicted with head and neck or esophagus squamous cell cancer. Compared with the approximately 20% improvement in response rate that was observed in Phase II clinical trials in the US (Kirn, 2001), a Chinese phase III trial demonstrated a difference of about 40% (Xia et al., 2004). No adverse side effects were observed, either, aside from mild fevers. Encouraged, Sunway Biotech bought the worldwide rights to ONYX-015 technology from ONYX in early 2005 for millions of dollars (Pollack 2005). H101 progressed smoothly through the approval process by China's State Food and Drug Administration and was officially permitted in November 2005 to enter the market (Jia & Kling, 2006). H101 thus became the first oncolytic virus to be state-approved for clinical use anywhere in the world.

What accounts for this drastically different situation in China? It may be easy for us in the US to immediately express doubts over this almost effortless rise of oncolytic therapy and suspect that some kind of foul play involved. While foul play has not necessarily been rejected and the accusation is brought up repeatedly by critics (Jia, 2007), it is nevertheless useful to engage in an objective examination of the relevant factors.

First of all, cutting-edge technology along the likes of gene therapy did not suffer any sort of backlash in China like it did in US, following the highly publicized death in the Penn clinical trial (Jia & Kling, 2006). Instead, the atmosphere in China was quite favorable. The Chinese government itself promoted gene therapy research: Sunway Biotech's US\$30 million budget for development of H101 was derived from Shanghai Industrial Co. Ltd., the mother company of Sunway Biotech that is also a state-owned corporation (Jia, 2007). The importance of social attitudes to scientific research is very much apparent here.

Furthermore, the number of clinical trials had almost quadrupled since 2003 to 19 in 2006 (Jia, 2006). As a rising superpower, China has clearly pushed for the expansion of its relatively weak biotechnology industry, already claiming the title of the first nation to approve oncolytic therapy. This situation fits seamlessly with the trend of balance-of-power politics that is also coloring the arena of global health policy (Fidler, 2008). Evidently, the role of research in the setting of international politics has also contributed to the smooth journey that oncolytic viruses have traveled in China.

In addition, researchers in China have a much easier time than their American counterparts in recruiting enough participants for the purpose of conducting large-scale clinical trials. Indeed, a population of over 1 billion, combined with poorer health infrastructure, ensures an abundance of willing, available participants in the country. Considering that the existing

health system does not cover expenses for most cancer treatments, Chinese researchers can gather large numbers of cancer patients quickly and cheaply (Jia & Kling, 2006). Here, then, is a familiar focus on “time, speed, and profitability,” echoing Adriana Petryna’s discussion of global experimentality. Much like how clinical research organizations hired by Western pharmaceutical companies choose participant populations and adjust trial conditions to demonstrate the most significant benefits for drugs (Petryna, 2009), similar sorts of clinical trial “games” are likely carried out in China.

Unlike American pharmaceutical companies, however, which can no longer effectively utilize Americans for drug trials due to their over-pharmaceuticalized bodies (Petryna, 2009), the Chinese trials can be conducted on Chinese soil with Chinese participants. This greater proximity, so to speak, is an advantage that can, in a way, more legitimize the results of Chinese clinical trials.

Then on a technical level, there are notable distinctions between regulations for clinical trials in China versus in the US. For instance, American researchers are mandated to immediately reduce fevers in participants of clinical trials, but such a requirement does not apply to Chinese researchers. Hu Fang, the president of Sunway Biotech, reasoned that allowing manageable fevers to persist in participants enhances viral activity—after all, adenoviruses naturally induce fevers in humans and may be more accustomed to such environments (Interruptus, 2006). This examples illustrates that simple differences in regulation can themselves cause different results.

Additionally, response rate in Chinese clinical trials is measured through tumor reduction, whereas researchers must show a survival benefit in American clinical trials. For head and neck cancers, increased survival due to an intervention is especially difficult to demonstrate, given

that afflicted patients live on for years with the tumors. Frank McCormick, the biochemist who founded ONYX, has called the Chinese definition of response rate a looser requirement of efficacy (Jia & Kling, 2006). Evidently, there are underlying value differences between Chinese and American conceptions of “what works” in cancer therapy and which deserves greater focus, direct reduction of cancer or survival.

Nor is there an emphasis in China on understanding precisely how H101 works in the body. In the United States, hoopla surrounding the death in Penn’s gene therapy trial has increased the need to unravel the precise activities of adenoviruses in the body, and the uncertainty regarding interactions between E1B 55-kDa and p53 has also been construed as a major obstacle in development of the therapy (Yamamoto & Curiel, 2010). This is a rather risk-averse stance, in that details surrounding the treatment must be completely filled in before the treatment can be widely applied. In contrast, the attitude in China appears more open: if it works, then it works, and its use should be allowed.

Such a laxer mindset had previously existed in the United States as well; notably, interventions like smallpox vaccination and the use of penicillin had been widespread before the mechanisms of action were properly understood (Wynder, 1994). Yet the focus has since shifted to dissection of mechanisms, whether it be development of a disease or how a treatment functions. Of course, there are critics who oppose this emphasis: the physician and public health researcher Ernsnt Wynder employs historical examples to argue that disease prevention measures often drastically reduce incidence rates decades or centuries before scientific details are fleshed out (Wynder, 1994). Thus he calls for an improved balance between basic science research and a push for prevention strategies.

By bringing up prevention of disease only now, I seek to highlight the fact that some topics are consistently missing from discussions of a cutting-edge technology like oncolytic therapy. Immersed in debates over the intracellular effects of cancer-killing adenoviruses, one can easily forget basic facts about cancers. Rarely is prevention mentioned, even though according to the World Health Organization (WHO), a third of all cancer in the world can be prevented by addressing key risk factors, including tobacco use (considered the most important risk factor), alcohol use, being obese or overweight, fruit and vegetable intake, etc. (WHO, 2009). Also missing are mentions of prevalence, distribution and projected trends associated with cancer: currently cancer is the top cause of death worldwide, with over 70% of the deaths occurring in low- to middle-income countries, and the disease is expected to kill an increasing number of people over time (WHO, 2009). Evidently, the bigger picture becomes more apparent once one steps outside the bounds of primary scientific literature.

An amalgam of factors contribute to this gap. Practically speaking, scientists must concisely yet thoroughly present their findings in publications. For instance, the most prestigious journal in the international scientific community, *Nature*, imposes a strict limitation of five pages on original articles (Nature Publishing Group, 2010). Thus the entirety of the allotted space must be dedicated to presentation and discussion of findings, aside from a succinct introduction in the beginning: there is simply no space left over for big picture considerations.

At the same time, reflecting on the topic at hand on a larger scale can diminish the significance of one's findings. While the discovery that E1B 55-kDa does not actually inhibit the intracellular p53 program was very important to individuals concerned with the development of cancer-fighting adenoviruses, in the global scheme of things, this finding may not appear so noteworthy. Yet applications for grants, on which scientists depend to fund their research, are

written precisely to highlight the significance of one's investigative goals (Alison Gammie, PhD, personal communication): this principle is made clear to people who newly enter biological research. In this way, these external factors encourage narrow scopes among scientists.

Indeed, much of the basic science research related to oncolytic adenoviruses operates at the level of cells, and cancer as a disease is dissected to microscopic detail. Much like Lewontin has stated earlier, complex processes are broken into “bits and pieces that can be isolated and that have properties that can be studied in isolation” (Lewontin, 1992). My own research supports this claim: for my senior thesis, I will study the influence of E1B 55-kDa on immune response in human cells. Anthropomorphically speaking, it is as if the cells are my patients, into whom I inject oncolytic adenoviruses and then measure the reactions of the immune system. As for real live patients in clinical trials, it seems to me that they are viewed as containers of complicated interplays between biological components that must be disentangled by researchers. I even sense that the human body is what is actually perceived by scientists as threatening to the oncolytic viruses, and not the other way around—the viruses must be tweaked to cleverly maneuver the body's immune defense in order to achieve their goal of killing the tumor cells.

Despite the wealth of information on what happens inside the body upon infection by engineered adenoviruses, so-called human data remains missing. This sort of data is composed of the intricate human stories behind (and beyond) statistics and scientific data that one is accustomed to seeing in peer-reviewed publications (Joao Biehl, personal communication). Additional information on participants tends to become available following unfortunate accidents in clinical trials, as the death of Jesse Gelsinger has already demonstrated. Mostly, this is a protective mechanism following ethical considerations of patient confidentiality (Gordis, 2009). Yet portrayals of participants (with their permission) will help humanize the treatment, which is

after all meant for human beings. Did the participants who received the cancer-killing adenoviruses express any fear about welcoming a foreign, unknown agent into their bodies? Did the participants understand the concept behind the therapy? Which kind of cancer treatment did they consider ideal? These are some issues that one can probe to gather humanistic information related to oncolytic therapy.

To this end, the approval of H101 (now marketed as Oncorine; Jia, 2007) in China is a beneficial development for the same field in the United States. Several American scientists have noted this already (Interruptus, 2006). The therapy's introduction into the market makes China a fertile ground for gathering more information on the treatment's effectiveness, as well as valuable human data. What's more, H101 currently is beyond the reach of most Chinese cancer patients, as it is sold for 3680 yuan (approximately \$460) per dose (Jia, 2007). Will the treatment be made more accessible and if so how? What are the reactions of people who have access, as well as people who cannot access the therapy? And perhaps most importantly: is it all worth it? In other words, should a resurgence for the field of oncolytic therapy be encouraged in the United States? Basically, China can serve as a surrogate for the United States as the location for "phase IV trials" (i.e. postmarketing surveillance; Gordis, 2009) on adenoviral therapy. Certainly the population and cultural differences cannot be overlooked, but seeing how the situation plays out elsewhere would provide excellent lessons for the field's future directions in the US and beyond. This also reveals that the situation between China and the US with respect to adenoviruses is more convoluted than just a straightforward framework of rival superpowers.

In the meantime, researchers in the United States will continue their basic science research on solving molecular-level mysteries of adenovirus functions. As one among them, I resolve to keep in mind the larger forces that shape my work: this is not to undermine my own

investigations but rather to situate them. I also seek to remember the gaps in evidence that are consistently present—though these will be better filled by individuals in other disciplines like anthropology. Conversations with fellow labmates in Dr. Flint’s Lab encourage me that other scientists are embracing the big picture as well.

Overall, the case of adenovirus-based cancer therapy illuminates the interactions between varying actors and forces in different spheres to shape the technology and its application.

Exploring the matter has produced a wealth of insights that I believe both individuals within and outside the field can benefit from.

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