Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 5

ZMapp: The Ethics of Decision Making

The development of treatments for human viral diseases consists of two quite different approaches. The first is research at the molecular level to define the virus' life cycle in its quest to produce progeny virus and then screen for pharmacologic drugs that block reproductive stages of that life cycle. To gain knowledge of what self-components the virus requires to allow its survival and production of progeny while interacting with the host, enormous computerized libraries of known chemicals or synthesized compounds are searched. The goal is to identify molecules with the ability to block viral replication. Such assays require a robust readout and automation involving robotics to screen virtually millions of test molecules to identify just a few that show promise. Any molecule identified requires, first, confirmation and, then, analysis that it is not toxic by itself. Thereafter, chemists study and modify its structure to optimize the therapeutic index, that is, the relative safety of a dose or treatment as opposed to its potentially harmful effect.

Achieving the maximal advantage for an eventual therapeutic product requires vigorous chemical and biological testing to evaluate the stability, half-life, and best route of delivery—either oral, intravenous, or subcutaneous. Armed with this knowledge, the developers' next steps of discovery are to determine the pharmacologic molecule's effectiveness, usually first in cell cultures and then in animal models. For testing Ebola virus, animal models can include genetically modified mice, guinea pigs, or subhuman primates.

In the course of this search, hundreds of thousands of molecules are often screened before a therapeutic "hit" is uncovered. Unfortunately and frequently, the molecule or compound identified is disqualified because of its toxicity, insolubility, or delivery problems. Chemists then work to alter the structure of the selected compound to overcome such difficulties.

Ebola's Curse. DOI: http://dx.doi.org/10.1016/B978-0-12-813888-5.00005-6

The time involved can be and is usually long and the financial cost being great. Nevertheless, this approach has achieved amazing success over the last few years. Examples are discoveries of drugs that changed HIV/AIDS infection from a near-routinely lethal event (mortality >90%) to a 1% or less death rate for HIV patients who are medicated daily. However, these drugs are expensive and not always available in some countries. Similarly, the antiviral therapy recently discovered for chronic hepatitis C virus (HCV) now cures over 95% of such patients instead of the lifetime persistent infection their predecessors suffered. Additionally, the risk of developing liver cancer and needing a liver transplant is greatly diminished. Although anti-HCV therapy is initially expensive, compared to the former long-term hospitalization, likely transplant surgery, or cancer treatment, the long-term cost is modest and the value is great for patients as well as for the health care system.

In view of the successful outcomes with antiviral therapies, finding one or more molecules to combat ongoing Ebola infection seemed possible. An announcement had appeared that the small molecule, GS-5734,[1] an adenosine analog with antiviral activity, protected 100% of rhesus monkeys 3 days after initiation of a lethal Ebola infection. The virus tested was the Makona variant of Ebola, a virus isolated during the outbreak in Sierra Leone during 2014. Of further interest was the drug's effectiveness against other filoviruses (Marburg), arenaviruses (LASV), and coronaviruses (SARS). Despite its promise, though, this therapy still required testing for safety and, then, clinical trials in humans. The issues of large-scale manufacturing and pharmacokinetics still needed resolution to determine whether a drug, if produced, would be available for the next Ebola outbreak. It was not yet available for Dr. Khan.

The second approach in the development of treatments for human viral diseases is harnessing the host's immune response. The immune system has evolved to enable the host to resist invasion by organisms like, in this case, Ebola virus. Proteins in Ebola that trigger an immune response are called antigens (immunogens). A host's immune response to antigens can travel down two very different pathways. The most common and satisfactory one provides protection, controls the infection by either preventing it totally or lessening (attenuating) its effects, and induces a protective immune response. Such a response can

provide long-term protection from Ebola virus so that a repeated infection does not cause disease—sort of one and done. To mimic that scenario, a vaccine is created to prime the immune response by programming it to recognize and then rapidly resist the Ebola infection in an individual who later becomes exposed to a person, animal, or substance contaminated with Ebola virus. Vaccines developed against viruses like measles, mumps, smallpox, yellow fever, poliomyelitis have changed the human and medical landscapes in that they succeeded in reducing the morbidity and mortality of human viral diseases. This success stands as one of the greatest of public health advancements. For example, smallpox alone in the 20th century killed an estimated 300 million individuals, about threefold more than all the wars of that century, including World Wars I and II. Vaccination eliminated smallpox so that, in the 21st century, not a single case has emerged.[2] Similarly, if one is infected by Ebola and survives, that person is immune to reinfection. Indeed, during the 2013–16 Ebola outbreak, such "naturally immune" individuals, because of their resistance to reinfection by Ebola, often worked to provide care and transport patients.

How does the immune response evade or control viral infection? The immune system must discriminate between foreign antigens, such as viral proteins, that are not found in humans (nonself) and those antigens that are self (proteins in your own cells and tissues). Cross-reactivity of a person's immune response to the virus with the individual's own "self-proteins" can lead to an autoimmune (antiself) response—a response to *self*-components, and autoimmune diseases like lupus, multiple sclerosis, diabetes, or thyroiditis.[3]

After an initial exposure to viral infection, the so-called acute phase, a race is on between the virus, which is replicating rapidly, and the host's immune system, which functions first to limit the amount of virus made and second to clear the virus from the host. At stake is whether the virus can successfully replicate itself. To combat the virus, the host mobilizes and uses many weapons, that is, both the immunologically specific and nonspecific responses. The nonspecific factors are all early combatants against the virus and the cells it infects. Included in this group are natural killer lymphoid cells, phagocytic macrophages—large cells that ingest or eat viruses—and proteins in the blood called complement factors that are capable of interacting with

viruses and also destroying virus-infected cells. Important is the innate immune system that provides the initial defense against pathogens and primes the subsequent adoptive (T cell and antibody) immune response. The major players in the innate immune response are toll-like receptors, which recognize particular microbial patterns, and type 1 interferons (IFNs). Again, there are conflicting reports of whether IFNs are suppressed or exaggerated. Nevertheless, these innate systems are mutually complementary and are involved in developing the ensuing adoptive immune response. Type 1 IFNs upregulate molecules on cells that present major histocompatibility complex (MHC) molecules, molecules that code for self. MHC molecules are essential for optimal interaction with T cells. Following a virus infection or vaccination, major antigen-presenting cells (called dendritic cells) present segments of viral proteins (peptides) that become located within MHC molecules to naïve T cells, an action termed "priming." By this means virus-specific T cells are generated and expanded numerically. These T cells are made in the infected host for the specific control of a virus infection. Thus, the major combatants against viruses are antibodies and T lymphocytes, both of which mount the host immune response to Ebola, although the relative contribution of each is not unknown. However, in this battle, within 10–14 days after infection, either the replicating viruses or the host's immune response will emerge as the winner. If the immune response wins, viruses are vanquished, and the host survives with enduring immunity to that virus. However, if the immune response is overcome, the Ebola virus infection ends in the host's death or in a subset of individuals fingerprints of Ebola that can be found months later.[4,5]

What is the cellular (T cell) virus-specific immune response? The component parts are CD8+ and CD4+ T cells. The T stands for thymus-derived, and CD8+ or CD4+ indicates a specific molecule present on the cells' surface used to identify the cell. The thymus is a two-lobed gland of the lymphoid system located over the heart and under the breastbone. Lymphocytes formed in the bone marrow (hemopoietic stem cells) migrate to and enter the thymus where they are educated (mature) and are then selected to become either CD8+ or CD4+ T cells. CD8+ T cells function as surveillance and killer cells, which accounts for their name "cytotoxic T lymphocytes" (CTLs). They travel along the highways of blood vessels and wander among tissues throughout the body seeking cells that are foreign (not

like self), because they express viral proteins. CTLs then recognize, attack, and kill such cells. By this strategy they eliminate the factories making viruses. CD8+ T cells also release soluble factors like interferon (IFN)-γ and tumor necrosis factor-alpha (TNF-α) that also have antiviral effects but do so without killing the virus-infected cell. CD4+ T cells predominantly serve a different role. They release soluble materials (proteins) that help or induce bone marrow-derived (non-thymic-educated) B lymphocytes to differentiate and make antibodies. CD4+ T cells release soluble factors (cytokines) that also participate in clearing a virus infection and, uncommonly, CD4+ T cells may also kill virally infected cells.

In contrast to reacting against cells, antibodies react primarily with viruses in the body fluids and are, therefore, most effective in limiting the spread of virus through the blood or in cerebrospinal fluids, fluids that bathe the brain and spinal cord. By this means, antibodies decrease a host's content of virus and diminish infectivity. Antibodies lower the number of viruses thereby allowing CTLs to work more efficiently. Antibodies along with effector molecules like complement can kill virus-infected cells. However, this mechanism is relatively inefficient compared to CTL killing of virus-infected cells. Although over 100,000 or more viral antigens must be present on the surface of a virus-infected cell to achieve lysis by antibody, less than 10 viral antigens expressed on a cell and restricted by MHC are all that are needed for a CD8 T cell to do the job. Thus, during infection, the eradication of virus-infected cells is the primary job of CTLs, whereas antibody's main task is to curtail the spread of virus in body fluids.

Antibodies are made by differentiated B lymphocytes named plasmacytes. Once activated, such cells can pump out 100 million antiviral antibody molecules per hour.

Antibodies latch onto and neutralize viruses by one of several mechanisms: (1) antibodies can coat or block the outer spike protein of the virus that is required to attach to the cell and begin its entry into the cell. By this means antibodies can prevent infection. This is the major action of vaccination. (2) Antibodies can aggregate or clump viruses so that the net number of infectious particles is reduced. (3) With the assistance of complement, antibodies can lyse (disintegrate) viruses, and (4) antibodies can react with viral antigens on the outer membrane of the infected cells to limit the manufacturing or

transcription of virus molecules inside the cells, thereby restricting the amount of viruses made. Each antibody molecule generated acts on a specific antigen or target molecule of the virus.

When a host is initially exposed to an infecting virus or to a vaccine-containing viral antigens, antibodies specific for that virus as well as CTLs are generated. The CTL response is initiated on the first day of infection, expands over 100,000 to 1,000,000 times by doubling roughly every 12 hours with peak expansion 7–8 days after exposure. Thereafter, the quantity of these cells contracts and is maintained at 1%–2% of the total generated: these become immune memory cells. Immune memory T cells are rapidly stimulated and accelerated to respond when the same or cross-reactive infection occurs, i.e., they protect against a repeated infection by the same virus. Antibody responses peak after the CTL response, and unattached or free antibodies are often weakly detectable during the acute phase of infection. The number of antibodies then rises over a period of 2–4 weeks after infection, and they linger for years.

During an onset of acute viral infection, the mechanics of obtaining sufficient virus-specific CD8 T cells in humans to transfer into a MHC-matched individual is barely doable, even when attempted as a research study in a sophisticated clinical research center in an optimal hospital setting in the West. This task is not feasible during an Ebola infection in Africa. Yet, the transfer of convalescent plasma (plasma is blood from which red cells have been removed) harvested from Ebola-immune donors into acutely ill Ebola patients is possible. Such "immune" plasma (plasma containing antibodies to Ebola) can be placed in storage and thus remain available. The million dollar questions are—does this protocol work and, if so, is it of therapeutic value. For such transfers, blood is harvested in heparinized tubes to prevent clotting. T cells, red blood cells, macrophages, etc., are removed by centrifugation, and the resultant plasma is injected intravenously into the infected patient. In clinical trials with 84 patients of various ages acutely infected with Ebola virus, 200–250 mL of inoculum was tested. This plasma was harvested from previously infected Ebola patients who survived the disease.[6] Unfortunately, though, the survival rate of patients in the trial did not improve significantly over that of the controls who were not so-inoculated. However, the study was flawed in that neutralizing antibodies to Ebola were not quantitated or adjusted

in the transferred plasma. Thus, exactly why the trial failed is not clear; was the entire procedure flawed or was the concentration of neutralizing antibodies in the plasma simply too low.[6] In other studies, potent neutralizing antibodies against Ebola were isolated from B cell clones of immune individuals who had recovered from Ebola infections. One such antibody, mAb114, given only once, protected 3 of 3 macaques even when administered as late as 5 days into the infection cycle.[7] The one macaque given no neutralizing antibody died at day 10 postinfection with 10^8 logs of virus. Similarly, potent neutralizing antibodies were isolated from a survivor of the 2014 Ebola outbreak, and 77% of the 349 monoclonal antibodies isolated neutralized Ebola indicating that a broad diversity of B cell clones target sites on the Ebola glycoproteins generated during infection.[8] Impetus to develop this strategy further came from these results with Ebola, and the same method was used in other animal/virus models. For example, monoclonal antibodies proved to protect guinea pigs from hemorrhagic arenavirus (Junin) infection of Argentina[9] and anti-HIV-1 antibodies prevented that infection in a monkey model.[10]

An important consideration underlying the proposed development of an Ebola vaccine was the fact that human survivors of the initial infection resisted reinfection when later exposed to Ebola. Such observations provided the scientific rationale and the logic for financial investment by government agencies like the National Institutes of Health (NIH) and charitable foundations to obtain an effective vaccine against Ebola. Less attention came from large pharmaceutical companies whose perspective was commercial. That is, even if successful, the vaccine would be used in as yet, nonindustrial (still third world) countries; therefore, the market for that vaccine would be smaller and less profitable than in industrialized Western countries. Also, because of its highly lethal nature, Ebola would require specialized facilities for handling and testing. Finally, insufficient data were available about the early events in human processing of Ebola virus infection.

As vaccines were considered, four Ebola-infected survivors undergoing the postacute phase of infection had been air-lifted from West Africa to Emory University School of Medicine. The profiles of these subjects' blood were analyzed at Emory and at the CDC in selective BSL-4 facilities. Surprisingly, the individuals displayed exceptionally strong anti-Ebola T and B cell responses.[11] These observations were

the opposite of early reports that T and B responses were suppressed. The cause of this difference could be temporal, that is, the timing of blood sample collection, the advanced methodology used,[11] or perhaps the survivor population studied. Analysis of specific anti-Ebola T and B cell responses during the early acute phase of disease is currently unresolved. With new and better facilities in West Africa, especially Sierra Leone and Kenema Government Hospital (KGH), recent NIH support to identify and map T cell epitopes (regions on the virus as it comes to the surface of infected host cells) and funding for virologists and immunologists from both Sierra Leone and the United States, solutions should soon be forthcoming. The importance will be not only in identifying which arms of the host immune response function during Ebola infection but also in discovering the essential viral proteins to constitute a vaccine that provides optimal immunity and protection.

This background brings us back to the advancing death of Dr. Humarr Khan from Ebola virus infection, the controversy about using ZMapp for his treatment and the ethics of administering an untested drug to severely ill persons. ZMapp was a cocktail of monoclonal antibodies, the first to be suggested 2 years earlier as a potential transfer antibody therapy for Ebola.[12] ZMapp, created through international cooperation, showed promising results in primates but had not been tested on or approved for human usage. The majority of research to develop ZMapp was funded by the National Institutes of Health and Public Health Agency of Canada. When the Ebola outbreak began, the question of its use was raised, although it had not yet been deemed safe or effective for treating humans. Tests with monkeys infected with Ebola had shown a protective effect when they were given ZMapp at 3–5 days after infection.[12] Could ZMapp have a similarly protective effect in humans? Also, ZMapp had been produced in tobacco plants, a procedure used to expand its production. Would there be an issue of sensitivity to tobacco antigens for humans in therapy provided intravenously?

"The evidence presented here suggests that ZMapp offers the best option of the experimental therapies currently in development for treating EBO-V (Ebola virus) infected patients. We hope that initial safety tests in humans will be undertaken soon" Gary P. Kobinger of the Canadian Public Health Agency's National Laboratory for Zoonotic Diseases and Special Pathogens stated.

As Dr. Khan lay dying in the Doctors Without Borders Care Center in Kailahun, and the debate of whether or not to treat him with ZMapp was raging, over 480 miles to the Northwest in Monrovia, Liberia, at Samaritan's Purse ELWA Hospital, another crisis was unfolding. Samaritan's Purse, a Christian Relief Ministry, was coming to grips with the fact that two of its health care workers involved in treating Ebola patients, Kent Brantly, a 33-year-old physician, and Nancy Writebol, a care provider and missionary, showed clinical symptoms and signs of Ebola. The infection was confirmed by blood test. A hospital administrator for Samaritan's Purse, Lance Plyler, knew there were experimental drugs being developed elsewhere to combat Ebola. Losing no time he contacted a CDC official stationed in Monrovia to obtain names and places in the United States to seek the necessary therapeutics. Meanwhile, the infected and quarantined Kent Brantly was surfing the net with his laptop computer for a potential and possible therapy for Ebola. Brantly came across the report in *Nature*[12] that ZMapp, a cocktail of antibodies to neutralize Ebola, saved monkeys challenged with a lethal dose of Ebola even when they were several days into their illness. However, ZMapp had been tested only in cultured cells or animals and was not yet known to be harmless or effective in humans. Nevertheless, Brantly selected ZMapp as his choice. Was the material available? Lance Plyler contacted Gary Kobinger in Canada who was involved in the creation and testing of ZMapp. Plyler requested that the drug be sent to Samaritan's Purse Hospital for its immediate use. Kobinger informed Plyler that the nearest supply of the drug was only 480 miles away from the ELWA facility at the Doctors without Borders Kailahun Care Facility, where Khan was near death. Concerning Khan, the debate continued whether or not he should receive ZMapp. Plyler requested the drug and arranged for a helicopter to take ZMapp from the Doctors Without Borders Care Center to Monrovia.

The issue was the limited number of ZMapp treatments available. Only five doses existed in all of Africa and who should be selected to receive it. ZMapp had been sent to West Africa to the Doctors Without Borders Care Center in Kailahun primarily to determine how the drug would hold up in the African environment of heat and electrical power failures. The plan was to then return the drug to Canada and re-evaluate its antiviral efficacy: was it stable; was there a loss in potency? Although a promising anti-Ebola therapeutic, ZMapp had

not attracted robust funds for its development. In a CBS News interview, Dr. Jeffrey D. Turner, President and CEO of Defyrus, a private life sciences biodefense company that collaborated with public government public health agencies and military partners in the United Kingdom and Canada, stated "The challenge that many people don't appreciate is that our plans were to scale up this drug for 2015 and even then, small amounts for clinical trials. What has really happened with this outbreak is it's caught us in a position where we didn't have enough ZMapp available because no one would have bought it."

ZMapp was produced in a specific type of biologically engineered, genetically modified tobacco plant, *Nicotiana benthamiana*, grown at Kentucky BioProcessing in Owensboro, Kentucky. The genes encoding the monoclonal antibodies made elsewhere were inserted in these plants and the plants then produced large quantities of the antibody. However, the procedure required several weeks. Thus, in this environment the manufacture of ZMapp took up to several months. Production was comparatively inexpensive, since as many as 100 million doses of antibody could be made for $36 million. In addition to Kentucky BioProcessing, the biopharmaceutical companies involved in the development of ZMapp included San Diego-based Mapp Biopharmaceutical and Texas-based Caliber Biotherapeutics.

After Humarr Khan's infection with Ebola was diagnosed at KGH, he asked for a transfer to the Doctors Without Borders Clinical Center in Kailahun to avoid further demoralizing his hospital staff. By chance, Kailahan was the site where ZMapp was stored. The question being debated by the doctors at that time was, should ZMapp be used for humans and, if so, in whom? How would these individuals be selected? It was into this setting that the severely ill Khan's name entered the debate. Initially and under pressure from the Sierra Leone government to do something for Khan, already recognized as a national hero in that country, the physicians treating Khan and others involved were presented with an ethical and philosophical dilemma. What if the patient died as a result of an allergic reaction to ZMapp? ZMapp had not undergone clinical trials for safety and efficacy in humans. What if the treatment failed? Many believed that Khan should receive ZMapp because, in all of West Africa, he was the leading and best known figure involved in the war on Ebola. However, others were hesitant. Also, the fact that Khan was African brought

attention to the recent uproar that Westerners were subjecting Africans to lethal therapy.[13]

After a heated argument, the authorities in charge decided against giving ZMapp to Khan. That decision would be unpopular and not in line with the general requests for help advocated by Khan's government and specific requests of his colleagues. Garry and Sabeti applied pressure that he should receive the therapy. Khan's blood had already generated antibodies to the virus, indicating that his own immune system was beginning to work to combat the viral infection. However, as discussed above, early reports that the virus could suppress the immune system remained under reassessment, generating concern that the drug might affect his immune response.

Khan was denied the ZMapp therapy but not told of its potential benefit or that it was on hand. Representatives of Doctors Without Borders said he wasn't consulted because it would be unethical to inform him of the potential drug that was not available to him. One of Khan's close friends and fellow clinical researcher, Dr. Daniel Bausch,[14] strongly disagreed, "Dr. Khan is the ideal person to make an informed decision, and I feel strongly that he should have been asked if he wanted it or not…that's one area where, frankly, I am critical." Nevertheless, shortly after being denied the drug, Khan died.

The next day, despite the same concerns that prevented ZMapp treatment for the dying Khan, other infected individuals received ZMapp. The treatment that might have saved Khan's life was, instead, transported to Samaritan's Purse ELWA Hospital in Liberia and administered to two Ebola-infected health workers from the United States. This act created a strongly emotional response from the local population and the international community. Giving ZMapp to two Westerners who survived and not to Khan, an African who died, was highly controversial. Since not all those infected with Ebola die (mortality ranging 50%–70%), possibly the two Westerners would have survived without ZMapp. After all, many did. If Khan had been given ZMapp and died, would Africans be convinced he was used as a guinea pig to be tested with an experimental/unproved therapy without either formal local approval or approval by Western scientific and government committees? The two American recipients of ZMapp, Kent Brantly and Nancy Writebol, were members of Samaritan's Purse, the Christian Missionary in Liberia. A source from the NIH stated that

someone from the CDC contacted Samaritan's Purse and that an NIH scientist later informed them of the drug. However, no one knew if the drug would work or if the ultimate recovery of those taking the ZMapp was due to the drug. After receiving ZMapp, Kent Brantly showed remarkable clinical improvement, although, in contrast, after receiving the drug Nancy Writebol's condition worsened. However, both Brantly and Writebol survived, but may have recovered without the ZMapp—one does not know. The indisputable fact is that Humarr Khan died without receiving ZMapp when, with its therapeutic effect, he might have lived.

Many of the natives in West African lacked trust in international efforts to combat disease and Ebola. Strangely, since the reported outbreaks of mass Ebola virus infections, some groups of native Africans have expressed doubt that Ebola really exists. Others have voiced allegations that health officials purposely infected the populations to harvest their organs. Hospitals, health care stations, and workers have been attacked and stoned by mobs. Awareness, quarantine, and prohibition of touching people sick or dead from the disease have been viewed by many Africans as myths of Western propaganda. The African custom of touching and washing the body of a dead person prior to burial was being denied and led to resentment, demonstrations, and riots. Further, such public health measures are alien to their culture. Many West Africans believe in cultural superstitions and view Ebola as a curse rather than a pathogen, associating Ebola with witchcraft and sorcery brought there by foreigners. Some locals believe that doctors are killing Ebola patients as a punishment for sexual promiscuity. Fabio Friscia, UNICEF coordinator of the Ebola awareness campaign, explained that what was creating the greatest problem in controlling Ebola was the "behavior of the population."[15]

In Guinea, Liberia, and Sierra Leone the local population often attacked and disrupted health care workers, forcing them to leave treatment centers and hospitals. In one episode occurring in South-East Guinea, eight members of an Ebola disinfection and awareness team were killed with stones and machetes by fearful villagers. The members killed were part of a relief wing of the Christian and Missionary Alliance.

In August 2014, armed locals attacked a medical clinic in Liberia, in an area named West Point, where patients were quarantined. Locals

broke down doors, stole bloody mattresses, sheets, and equipment and caused patients to flee in a panic. The day before the raid, a crowd of several hundred locals drove away burial teams and police, chanting "No Ebola in West Point."

Violent attacks have resulted in Doctors Without Borders and medical volunteers having to withdraw from their posts because of concerns for their safety. A spokesperson for Doctors Without Borders stated "We understand very well that people are afraid because it is a new disease here, but these are not favorable working conditions so we are suspending our activities." [16]

Despite such difficult times, the story of ZMapp is not over. As both foreign as well as African health care providers and doctors continued to die from Ebola virus infection, the WHO endorsed the use of ZMapp to combat the uncontrolled outbreak. Liberian President, Ellen Johnson Sirleaf, in a direct request to President Obama, asked for a supply of the drug to be used for the treatment of local doctors.

Representing the producers of ZMapp, a spokesperson for Kentucky BioProcessing stated, "Though this is all relatively new and there's still a long way to go and a lot of things are going to happen as we go into drug-approval protocols with ZMapp...I think certainly it shows great promise that the tobacco plant can be utilized for such things. We'll see where that goes. We're certainly optimistic."[17]

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