Ideas in ACTION February 2012

SciTech Lecture: February 23, 2012
Featuring Steve Mizel and Bruce Kaylos

The title of this lecture was "*Vaccines: Why and How*". For the first time, the lecture series spotlighted two speakers who addressed a topic from differing perspectives. Just as the title indicates, Steve Mizel, Ph.D. spoke to the "why" of developing vaccines and Bruce Kaylos described the "how". Dr. Steven Mizel, Professor, Department of Microbiology & Immunology, Wake Forest University School of Medicine, opened the lecture by describing how important it is to develop new vaccines in light of global Bioterrorism threats such as Anthrax, Plague and Smallpox. He explained the history and significance of Bubonic Plague, its devastating effect in history and the danger it poses as a bioweapon. To be an effective weapon, a biological agent must be easily spread or transmitted from person to person, cause high death rates, cause public panic and social disruption, and require special action to prepare a population against specific attack. The bacterium that causes the plague is just such an agent.

A single bacterium, *Yersinia pestis*, is responsible for three types of plague depending on the route of infection. Bubonic Plague is the infection of the lymph nodes; Septicemia is the infection of the blood; and Pneumonic Plague is the infection involving the lungs. The bacteria are transmitted through fleas, from rodents to humans and the resulting disease causes heavy fatalities. This bacterium has been used as a significant and effective bioweapon through history. Infected corpses were catapulted into besieged cities in the 1300's and the Japanese tested a "flea bomb" in Manchuria during WWII. The disease manifests within a few days and begins with headache, fever, nausea and vomiting. As the disease progresses quickly through the human system it takes only days to cause death. If the bacterium is inhaled it can produce death within 48-72 hours.

Dr. Mizel described how the body's immune system defends against pathogens, disease causing agents in the environment. To mount a specific defense to a specific pathogen the body must have been previously exposed and survived the occurrence or must have been given a vaccine containing a weak form of the pathogen, killed pathogen, or specific components of the pathogen. The body creates antibodies against a specific pathogen that will target and destroy that pathogen when it invades the body. Immunologists like Dr. Mizel have found that there are molecules in our immune system termed Toll Like Receptors (TLRs) that serve as danger signals—alerting the immune system that a dangerous pathogen is present. A structure called a flagellum, a whip-like tail used for movement by bacteria offered Dr. Mizel's team of scientists an opportunity to develop a new way of making very potent vaccines. The major structural component of the flagellum, a protein called flagellin, can activate a TLR and promote a very strong protective response when the flagellin is added to a vaccine. Dr. Mizel created a novel vaccine using flagellin and two proteins produced by

the plague bacteria. Tests have shown that this vaccine dramatically increases the production of antibodies against plague. When mice are exposed to *Yersinia pestis,* the mice die within 3 days. However, mice given Dr. Mizel's vaccine all survive. In fact, they don't even look sick. Dr. Mizel concluded his lecture by dispelling some of the myths surrounding vaccines. They do not cause the disease they are designed to defend against. Although some people have argued that vaccines can cause autism in small children, Dr. Mizel stated that there is no scientific evidence to support this point of view. Furthermore, the disappearance of most childhood diseases is due to the availability of vaccines. Without vaccination, these diseases will most certainly reappear.

Bruce Kaylos, Program Manager, NCBIO Biotech Manufacturers Forum, stepped up to discuss the dynamics of developing vaccines. He explained that cultural trends are changing the process of vaccine development. Families are less centralized and people are far more mobile which means that bacteria will be distributed throughout a greater area and tracing it back to a source has become complicated. In some cases communication among international governments and companies must occur to address world health issues as opposed to issues surrounding a local outbreak which could be more easily contained. Additionally, societal perceptions of a new innovation determine whether or not the public will accept the new technology and treatment, or prevention, being developed. Just because a solution is available doesn't mean the public will automatically accept it or lead to widespread usage of that solution. People tend to be wary of new discoveries and slow to openly embrace changes they don't understand which alluded to the myths about vaccines that Dr. Mizel refuted.

Once researchers uncover an idea that could potentially provide a cure, treatment, or prevention for a disease, the pathway to the consumer is long, closely regulated and expensive. Mr. Kaylos provided a timeline that displayed the activity involved in that pathway and the customary amount of time each portion requires, easily ranging from six to ten years. The Food and Drug Administration (FDA) has in place stringent regulations about the level of quality pharmaceutical companies must attain at every level as they develop and test a new medicinal product. Another consideration is the type of company that will host the process. It could be a small startup company seeking funding from venture capitalists or an established corporation with its own resources. Not only will the infrastructure, facilities and workforce available for testing and producing a vaccine determine the optimal type of host company, but they will impact the cost incurred. The market demographics will influence the decision to continue forward or eliminate the drug from the pipeline. Without strong data indicating that the market would support a return on investment that perpetuates the process, a company cannot afford to pursue the product.

Mr. Kaylos then contrasted the character of biomolecules used in vaccine design to those used in other applications. In the case of vaccine development the biomolecules are not well characterized due to their heterologous and complexed nature and a broad range of molecular weights when purified. In addition, animal models are not always good predictors of the in vivo activity because they tend to have an indirect biological effect. In contrast, well characterized biomolecules used in other applications are homologous compounds or proteins capable of being highly purified with well-defined analytical assays for delineating a direct biological pathway to their effect. These differences create a more complicated and intricate process for vaccine development with more variables to be considered.

Once the vaccine has reached a point where it can begin to be administered to humans, the FDA has a multi-segment clinical trial regime of testing. This will require additional years to complete before it reaches the production for market phase. Not until all these steps have been completed and the results have met with FDA approval can the agent responsible for development begin to receive reimbursement for the expenses incurred during the process. But even after the product is marketed, the public may be slow to accept its use causing that recapture of expenditure to be sluggish.

Mr. Kaylos concluded the lecture by discussing the future of vaccine development. He mentioned personalized medicine which would limit the level of marketability for each drug because treatment would be based on an individual's genetic make-up as opposed to the drug being used as a blanket prophylactic or therapeutic solution for the masses. The benefit is that treatments can be specifically targeted to individuals that will truly respond to the therapy. Other therapies can be more rapidly and effectively developed for individuals who did not respond well to the initial therapy. Providing better overall health care success will also decrease the life cycle of drugs and thereby limit the quantity manufactured. This could mean that there will be fewer "blockbuster" drugs developed, but the overall successful treatment of a greater spectrum of diseases will be enhanced. Such examples in the evolution of drug development spotlight the need for novel approaches to regulatory approval and a more flexible workforce with extended capability to meet the changes. These challenges do not spell doom and gloom for healthcare, but demonstrate the specialization and enhanced treatment that will be utilized in the future to develop more treatments and preserve an adequate revenue source for the continued growth of the industry.