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PORTRAIT

Portrait of Dr. Ted M. Ross

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I have always been interested in science since I was in grade school. I clearly remember my father and I making a poster of how the moon rocket propelled itself into space describing each of the stages of separation as it traveled to the moon. We examined how the lunar lander made its way from the rocket ship to the Moon and back. I was fascinated with how it worked. This curiosity carried over to many areas of science, including how the human body worked, the cells and DNA that made each organism. And in particular, how we protected ourselves from infectious agents. I entered college at the University of Arkansas in the early 1980s at the explosion of molecular biology and it revolutionized our understanding of cells, immune system, and the interactions with infectious agents, and how devastating these agents can be to the host. I attended a lecture in 1984 by a microbiologist at the University and he described to us this newly emerging disease, which was to become known as AIDS, caused by a virus, the Human Immunodeficiency Virus or HIV. A virus that attacked our own immune system, in order to replicate and spread, causing a unique and deadly disease. After completing my Master's degree in Microbiology, I wanted some "real-life" experience and chose to work at the Medical Center in Little Rock in the research laboratory of Dr. David Davies. He showed me what it was like to be a medical researcher in academia in the United States and it inspired me to apply and be accepted to the Graduate Program in Microbiology and Immunology at Vanderbilt University. I spent 5 y working in the laboratory of Dr. Patrick Green on a dissertation project focused on a retrovirus that caused cancer in infected people (HTLV). The ability of a single protein of this virus, that when expressed in human cells, would lead to a malignancy was fascinating to me. I learned the techniques in molecular biology and cell culture that I still use to this day and owe a debt to Dr. Green for all he taught me. I was his first graduate student and I did not realize it at the time, but know now, that I was in a special position in his laboratory because he had the time and energy to work with me directly to train me on not only technical issues of science, but also how to think like a scientist. I have tried to emulate this level of training and involvement in my own student's graduate and postdoctoral mentorship. At Vanderbilt, an entire new world of bacteria, viruses, yeast, and other microorganisms were presented to me and in turn, how our own immune system responds to these foreign invaders.

In 1997, I entered the laboratory of Dr. Bryan Cullen at Duke University where I used these molecular biology skills to address some of the questions around the newly discovered coreceptors for HIV entry into human cells. It had been known that the envelope protein of HIV used the CD4 receptor to enter immune cells. However, there appeared to be differences in different strains of HIV and how they entered cells and it appeared that there was more for entry than CD4. These coreceptors turned out to be chemokine receptors. I focused on understanding the domains on the envelope and the chemokine receptors CCR5 and CXCR4 for binding and entry into human cells. My skills in molecular biology and the ability to manipulate the HIV genome caught the attention of Dr. Harriet Robinson at Emory University who had just moved to Atlanta to be part of the newly formed Emory Vaccine Center. Dr. Robinson brought her expertise in DNA vaccination and avian retroviruses to AIDS vaccine research and was looking for skilled researchers to design new generation of HIV/AIDS vaccines. I joined a group of talented post-docs and senior researchers involved in designing DNA and VLP based vaccines for HIV. In order to improve the effectiveness of HIV envelope-based DNA vaccines, I used a molecular adjuvant co-opted from the complement immune system called C3d. I designed several HIV envelope-C3d fusion genes and expressed them from DNA vaccines in mice to enhance both envelope antibody titers, but also the neutralizing titers. This was the first of many vaccines that would be designed by me or by my laboratory members over the next 17 y. I used this technique for improving the antibody titers for antigens from several pathogens, including influenza.

In early 1998, many viral samples were being shipped to the Centers for Disease Control and Prevention in Atlanta from an outbreak of avian influenza in people from a newly emerging subtype, H5N1. I started working on understanding why these new strains were so deadly. This initial research in influenza, along with our continued HIV vaccine research were the basis for my establishing my own laboratory and research program in vaccine research and development initially at East Carolina University and in 2003 at the University of Pittsburgh. At this time, most of the laboratory was focused on designing an AIDS vaccine using consensus designs of the HIV envelope to elicit broadly-reactive neutralizing antibodies against the great diversity of strains of HIV. Using virus-like particle vaccines, our research group learned quite a bit about how to design consensus sequences to effectively elicit these kinds of responses. However, as the field has learned over the years, HIV vaccine design is challenging and each step has been slow and

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About Dr. Ross

Ted M. Ross did his undergraduate and graduate studies in Zoology and Microbiology at the University of Arkansas in 1982–9. He received Doctorate from Vanderbilt University in 1996. He was awarded the inaugural Sidney P. Colowick Award in Outstanding Graduate Research. Dr. Ross performed a post-doctoral fellowship for 2 y at Duke University on HIV biology of viral entry and 18 months at Emory University on vaccine development for HIV and influenza viruses. He then started his own laboratory as Principal Investigator at East Carolina University and in 2003 moved the laboratory to the University of Pittsburgh in the Departments of Medicine-Infectious Diseases, Microbiology and Molecular Genetics, and as a founding member of the Center for Vaccine Research. Dr. Ross is currently the Director of the Center for Vaccines and Immunology and Professor in Infectious Diseases at the University of Georgia. He is the Georgia Research Alliance Eminent Chair in Emerging and Zoonotic Pathogens. He is a scientist with experience in the fields of virology, vaccines, immunology, and microbiology. Dr. Ross' research focuses on designing, developing and testing vaccines for viral diseases often at the interface of zoonotic and human interface, such as influenza, but also dengue, chikungunya, respiratory syncytial virus and HIV. He is the senior investigator that developed computationally-optimized broadly reactive antigen (COBRA) technology for the universal, rational design of vaccine candidates for influenza viruses. He and his laboratory has developed DNA, recombinant protein and virus-like particle (VLP) vaccines for pandemic and seasonal influenza pre-clinical and clinical research trials. He has multiple high impact publications in pre-clinical vaccine assessment in mice, ferrets, and non-human primates, is the primary investigator on externally funded research projects. He is conducting his research with external funding from a variety of federal agencies, foundations and corporate sponsors. In 2013, Sanofi-Pasteur licensed the COBRA HA vaccine technology for its Universal Influenza Vaccine Development Program. Dr. Ross has published more than 130 papers and book chapters on infectious disease and vaccine development. He has been an invited speaker at more than 100 national and international conferences and participates in several vaccine working groups, including at the NIH, Centers for Disease Control and Prevention and World Health Organization. He is an Editorial Board member of *Vaccine*. He previously served as Editor-in-Chief of the journal *Current HIV Research*. In addition, he has been an *ad-hoc* reviewer on NIH study sections and a reviewer for 14 different journals. He served as the Treasurer of International Society for Vaccines from 2012–2015 and now is the current Secretary (elected 2015) and has served as the Co-Chair of the 8th and 9th Vaccine and ISV Congress in Philadelphia (8th) and Seoul (9th).

sometimes painful. Most vaccines against HIV infection have not been successful and the studies continue in our laboratory. But the basis for consensus design of antigens yield us some good ideas that we felt would be useful in designing vaccines for other viral antigens and decided to apply them to influenza.

Over the next decade, research activities in influenza began to grow and with each new funding award and publication in influenza vaccines, our research group started to become noticed by the research community. In 2006, I was asked to join the new Center for Vaccine Research at the University of Pittsburgh as one of 2 founding laboratories to fulfill a mission to design and develop new vaccines against emerging and re-emerging pathogens. My laboratory undertook this mission with vigor and decided to focus on influenza. As H5N1 highly pathogenic avian influenza began to re-emerge in late 2004/early 2005, our research group began to focus on how to address a fundamental problem in influenza vaccine research: how to design a vaccine against strains of influenza that do not yet exist. This issue is at the core of both seasonal influenza and pandemic influenza vaccine development. We decided to use H5N1 influenza as the prototype to design a strategy to elicit a broadly-reactive immune (antibody) response against all strains of H5N1 influenza regardless of the clade or subclade of H5N1. Antibodies elicited by a strain in one clade of H5N1 do not efficiency neutralize strains of other H5N1 clades. There are currently 10 clades of H5N1 that strains of this subtype are classified based upon phylogenetic sequence of the hemagglutinin (HA) protein. Currently, strains of this subtype do not transmit among humans, but it has been determined that as few as 5 amino acid changes in the HA molecule are necessary to transmit between ferrets (and therefore people). At first, we designed a consensus sequence for HA, the primary neutralizing target of antibodies, but quickly realized that the number of sequences for HA for H5N1 strains in public databases were limited, compared to our previous experience with HIV envelope sequences. In the mid-2000s, there had been fewer than 400 fatal cases of H5N1 infection in humans and almost all of those infections were attributed to viruses in clade 1 and clade 2, which made up 90% of the HA sequences in the database. However, a future H5N1 human transmissible strain could evolve from a strain from any of the 10 clades. If we designed a consensus using the current strains in the database, the final sequence would be biased to sequences in one or 2 clades, would have similarity to most dominate clade (clade 2), and would not represent a vaccine candidate for all of strains in the H5N1. Therefore, we decided to use a new approach led by a talented graduate student in my laboratory to perform a layered consensus approach with multiple rounds of consensus building with first, second, and third generation of sequence building to eliminate the bias in sequences in these public databases. We termed this new approach COBRA, which stands for computationally optimized broadly reactive antigen.

My laboratory successfully demonstrated the protective efficacy of these COBRA vaccines against H5N1 challenges in mice, ferrets, chickens, and non-human primates in a series of publications. With this success, in 2010, we engaged with the large influenza vaccine manufacturer, Sanofi-Pasteur, began collaborating to use COBRA techniques for the development of a seasonal influenza vaccines that would elicit broadly reactive

antibodies against H1N1, H3N2, and B influenza. Development of these types of broadly-reactive or "universal" influenza vaccines is currently the focus of the influenza vaccine research and vaccine manufactures. The goal of a truly universal influenza vaccine is to elicit protective immune responses that prevent disease in the infected individual and blocks transmission of nascent influenza viruses to other people with different pre-immune backgrounds. To achieve this goal, a universal vaccine will need to be effective in all populations of people and elicit long-lasting durable immunity to eliminate the need for annual influenza vaccinations. Developing a universal vaccine strategy for seasonal influenza subtypes has the potential to greatly impact human health. A vaccine that protects against influenza variants within and across subtypes will improve our understanding of the basic biology, evolution, and transmission of influenza A virus. There are greater than 40 universal influenza vaccine candidates in development, but almost all of them elicit immune responses that only modulate influenza-induced disease, but the challenge is daunting and the process may need incremental steps to achieve. COBRA HA-elicited antibodies have HAI activity against the receptor binding site, which has benefits over other universal vaccine candidates. Induction of HAI antibodies is accepted as a surrogate/correlate for protective efficacy in humans. Therefore, COBRA-based vaccine candidates have a clear path forward to clinical proof of concept unlike many other universal vaccine candidates. Universal influenza vaccine approaches have the potential to be paradigm-shifting for influenza vaccine landscape, with the goal of replacement of seasonal vaccines with univ-ersal ones specifying enhanced efficacy through breadth, and potential for increased durability through the use of adjuvants. The ability of COBRA HA designs to elicit HAI responses against future antigenically distinct H1 viruses for which the current H1 component is a mismatch will provide a critical assessment for their feasibility as "subtype universal" vaccine candidates.

In 2015, I accepted the position as the Director of the Center for Vaccines and Immunology (CVI) at the University of Georgia and have embarked on a 5-year development plan to create a Center focused on influenza and other pathogens at the zoonotic and human interface. As globalization and other environmental changes alter the dynamics of disease spread, emerging, re-emerging and zoonotic diseases pose an increasing risk to global public health, animal health, and global security. To meet the increasing need for new vaccines and vaccine strategies, the CVI was established at the University of Georgia. The center will facilitate basic and translational research that addresses the "Science of Vaccines" and the critical need for new and improved diagnostics, adjuvants, therapeutics and vaccines for both existing and emerging infectious disease threats. The University of Georgia is uniquely qualified to accommodate a Center for Vaccines and Immunology because it currently has diverse, world-renowned expertise within the areas of infectious disease, veterinary medicine, ecology and public health. By engaging the world-class biocontainment resources at the University of Georgia and the expertise of surrounding institutions, the CVI can focus on emerging and re-emerging zoonotic infections, including biodefense agents. As the lead research laboratory, we will continue to develop and expand our COBRA vaccine program into the clinic and expand our unique research strategies to other pathogens. In addition, with the hiring of new faculty, we are building a team of researchers to address vaccine development for global pathogens with a strategy of designing, testing, licensing, and marketing novel vaccines for to address global health.