Personal Statement

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DEPARTMENT: Microbiology and Immunology
AREA OF EXCELLENCE: Research

I joined Indiana University School of Medicine-Northwest (IUSM-NW) on April 1, 2006. Since that time, I have published 11 papers (3 as corresponding author, 1 first author, 4 second author, 1 third author, 1 fourth author and 1 fifth author) and a book chapter. Among the papers, three are based on work completed during my postdoctoral training and eight are based on work conducted in my own laboratory. Of the eight papers, while five have resulted from collaborations with other scientists, three are from my own research program. I currently hold two extramural grants [NIH RO1 grant (5 yr, $1.5 million total budget) and a Scientist Development Grant from American Heart Association (4 yr, $308K total budget)] and have finished one intramural grant (Research Enhancement Grant from Indiana University). Since 2006, I have been teaching Medical Microbiology to 2nd year medical students with an overall assessment score of 4.42 (Discipline average = 3.69). I have also served as a member of the animal care committee and the radiation safety committee, an editorial board member of the Journal of Bacteriology and Parasitology, and a vice president of the Korean Scientist and Engineer Association-Midwest. Details on my accomplishments are described in the sections below.

Research

Time devoted: 75%

Independent Research

The main target of my research is the bacterium *Staphylococcus aureus*. This bacterium is found mostly on skin, anterior nares and other mucosal surfaces of approximately 30% of the human population and can cause a variety of diseases ranging from soft-tissue infections to life-threatening diseases such as endocarditis, toxic shock syndrome, and necrotizing pneumonia. To the public, the bacterium is widely known as MRSA (**m**ethicilliln **r**esistant ***S. aureus***). In 2005, this bacterium killed more people in the US than did HIV (human immunodeficiency virus). Research in my laboratory focuses on 1) identification of staphylococcal genetic systems important for pathogenesis of the bacterium, 2) discovering the molecular mechanism of the systems, and 3) development of drugs to interfere with the systems as therapeutic measures. The bacterial genetic systems we are currently studying are "SaeRS two component system" and "carbon catabolite repression system".

1. SaeRS two component system

Two component system (TCS) is a signal transduction mechanism by which bacteria adapt their behavior or gene expressions in response to environmental challenges (e.g., nutrient concentration, salt concentration, or the presence of immune cells). Using the SaeRS system, *S. aureus* surveys its surrounding environmental conditions and alters its gene expression, mostly

toxin and enzyme production, to maximize its survival. The SaeRS system is composed of sensor kinase SaeS and response regulator SaeR and the two other proteins, SaeP and SaeQ, whose functions are completely unknown. Although it is well established that the system is critical for bacterial survival in host, the signaling mechanism of the system is largely unknown. For the last two years, we have made the following progress in understanding the molecular mechanisms of the system: 1) SaeR binds to the DNA sequence GTTAAN$_6$GTTAA (N= any nucleotide); 2) Phosphorylation of the SaeR by SaeS is essential for DNA binding; 3) SaeR binding to target DNA is essential for transcription of genes; 4) *S. aureus* has 21 genes with perfect SaeR binding site and 135 genes with imperfect binding sites carrying one nucleotide mismatch. We published these results in the Journal of Bacteriology [vol. 192(8)] in 2010. Recently a small peptide called aureusimine was reported to activate the SaeRS system; but we found that the authors used a strain with an insertion mutation in the SaeRS system. We showed that the apparent regulation of the SaeRS system by the peptide was an artifact from the mutation. We published these results in PloS One in 2010. Currently we are studying the role of the other two proteins, SaeP and SaeQ, in signal transduction. From this study, we submitted another manuscript to Journal of Bacteriology and are preparing two more manuscripts.

2. Carbon catabolite repression system

Bacteria are well known for their efficient energy usage. For example, when more than one carbon source is available, bacteria consume the carbon source that can be rapidly metabolized (e.g., glucose) and shut down expression of the genes involved in utilization of other less desirable carbon sources (e.g., ribose). This phenomenon, carbon catabolite repression, is wide-spread among bacteria. In *S. aureus*, CcpA (catabolite control protein A) is carrying out the repression. Unexpectedly, we found that, in *S. aureus*, CcpA is also involved in proline synthesis. Being an amino acid, proline is a key building block in protein synthesis. Although *S. aureus* has all the genes necessary for proline synthesis, it is unable to synthesize proline. We resolved this paradox by showing that CcpA represses the expression of proline synthesis genes in the presence of rapidly metabolized carbon sources such as glucose. When a less desirable carbon source (e.g., ribose) is used as a sole carbon source, *S. aureus* can synthesize proline and, as a result, grow without exogenous addition of proline. We hypothesize that *S. aureus* uses glucose as an environmental cue to adjust their amino acid metabolism. Since both glucose and proline are available in human blood and body fluid, once *S. aureus* detects the presence of glucose, it shuts down expression of not only genes involved in utilization of other less desirable carbon sources but also proline synthesis genes, maximizing their energy efficiency. These results were published in Journal of Bacteriology [vol. 192(15)] in 2010.

Collaborative Research

As stated above, the main goals of my research are to find staphylococcal genetic systems important for the bacterial virulence and to develop therapeutic means to combat the bacterial diseases. To broaden approaches of my research, I have established extensive collaborations with other researchers in the Chicago area. Currently I am conducting the following 6 collaborative projects. Among them, four are initiated by me and the other two are by my collaborators.

Projects initiated by me

1. Genome-wide screens for *Staphylococcus aureus* virulence genes using a functional genomics technology (Dr. Hyunwoo Lee at University of Illinois at Chicago)

Dr. Hyunwoo Lee and his colleagues developed a functional genomics technology called MGK (**M**onitoring of **G**ene **K**nockouts), by which one can easily follow thousands of bacterial mutants with microarray assays. During my postdoctoral training, I developed a transposon mutant library for *S. aureus*. The library is composed of 1,700 mutants whose transposon insertion site is known. By applying MGK to our mutant library, we hope to identify the genes important for staphylococcal survival during animal infections.

2. The role of prophages in virulence of *S. aureus* (Dr. Scott Peterson, J. Craig Venter Institute)
   Prophages are viral genomes integrated in the bacterial genome. Recent studies have shown that prophages contribute to bacterial pathogenesis. Dr. Scott Peterson at the J. Craig Venter Institute is a world expert in bacterial genomics. In collaboration with Dr. Peterson, we are investigating whether prophages affect bacterial gene expression during infection processes.

3. Identification of novel antimicrobials from acidophilic soil bacteria (Dr. Seungbum Kim, Chung Nam University, S. Korea)
   Dr. Kim is a bacterial taxonomist in S. Korea and has been working in my laboratory since Aug. 2010 as a visiting scholar. His area of specialization involves isolation of novel acidophilic bacteria from soil. During his stay in my laboratory, he isolated bacterial species from soil in the Gary, IN area and found that some of them produce metabolites with antimicrobial activity against the *S. aureus* strain USA300, a clinical isolate of MRSA. The goal of this collaborative research is to test whether we can identify novel lead-compounds from acidophilic soil bacteria for development of new antibiotics with a broad spectrum of efficacy.

4. Application of nanotechnology to development of antibacterial agents (Dr. Elena A. Rozhkova, Argonne National Laboratory)
   When their size is reduced to nanoscale, many metals acquire unexpected characteristics. Some of the characteristics can be used to kill microbes. Dr. Rozhkoava is a nanoparticle researcher at Argonne National laboratory. Currently we are examining whether nanotechnology can be applied to the treatment of infectious diseases.

Projects initiated by collaborators

1. Antibacterial methionine aminopeptidase inhibitors (Dr. Qizhuang Ye, Department of Biochemistry and Molecular Biology, Indiana University)
   Dr. Qizhuang Ye at Indiana University is an internationally recognized expert in the field of bacterial methionine aminopeptidase. Methionine aminopeptidase is an enzyme that cleaves the first amino acid methionine from proteins. The methionine cleavage is essential for survival of many bacteria including *S. aureus*. Currently, Dr. Ye is developing inhibitors for the enzyme, while my laboratory conducts *in vivo* efficacy tests for the inhibitors. In 2011, Dr. Ye submitted an RO1 grant proposal for this study where my intellectual contribution to this proposal is 30%.

2. The *yhcRS* systems in *Staphylococcus aureus* (Dr. Chuan He at the University of Chicago)

The YhcRS two component system of *S. aureus* has been reported to be essential for the bacterial growth. We found that the system operates exclusively under anaerobic conditions and controls multiple genes involved in capsule synthesis, virulence, and carbon metabolism. The sensor kinase YhcS has 4 Fe-S clusters and their oxidation is a key regulatory mechanism of the system. Currently we are preparing a manuscript to publish these results.

Teaching

Time devoted: 20%

My major teaching responsibilities at IUSM-NW are to give lectures to 2nd year medical students in Medical Microbiology and to lead Problem Based Learning (PBL) sessions. In addition, I give a 2 hr lecture to 1st year students on antimicrobials and an overview of medical microbiology. In 2010, I devoted 22 hours to lectures, 56 hours to problem based learning session, 4 hours to review, and 13 hours to testing.

Early on, I realized that teaching medical students should be different from teaching graduate students. If a lecture topic is intellectually interesting but has no direct impact on their test scores, medical students tend to ignore it. However, fact-based logical thinking and application of scientific concepts in understanding clinical outcomes are vital for students to become competent physicians. For the last five years, I have tried to find the appropriate balance between helping students' test preparations and incorporating scientific concepts and methodologies into the teaching topics.

To make my lectures more relevant to the students' needs, I structured my lectures to include only the topics with direct implications to clinical situations. If a topic is scientifically very interesting but has no clinical relevance yet, I avoid adding this topic to my lectures. Whenever possible, I also try to show the connection between science and medicine. For example, when I teach the fact that *Mycoplasma* does not have a cell wall, I ask about antibiotics that cannot be used for *Mycoplasma* infections. Those discussions usually lead to the mechanism of action of antibiotics and the realization that certain antibiotics such as beta-lactams and vancomycin kill bacteria by blocking cell wall synthesis. Subsequently, we discuss why antibiotics cannot be used for viral infections but why certain antibiotics can be used not only for bacterial infections but also protozoa infections.

To assess the efficiency of my lecture delivery, I always give a quiz before and after each lecture. The questions in the quiz are directly related to the topics in the lecture. Since students give their answers by using the 'clicker system', I can see the results instantaneously. After my lecture, if students don't show a significant improvement in their scores, I take it as a sign of poor delivery of my lecture and find the solution for it.

So far, my lectures have been received well by students. For the past five years, the average overall assessment score of my teaching is 4.42 (discipline average = 3.69, school average = 4.17). Examples of students' responses to my teaching are as follows.

Dr. Bae was very helpful outside of class and was willing to give practice examinations

and help with understanding the process of answering clinical case type questions (2008)

Dr. Bae is one of the best professor that I have ever had. He does everything in his power to make sure that his students succeed in this difficult class. Words cannot express enough the gratitude that I have for all of his efforts (2009)

I can't say how awesome Dr. Bae is. He is a great teacher who cares about his students (2010).

I was elected as "Outstanding Basic Science Professor at Northwest by the Medical Class of 2010. I was also chosen to serve as a hooder for the class 2011.

In addition to teaching medical students, I have participated actively in teaching postdoctoral fellows and undergraduate students in my laboratory. From 2007 to 2010, I have mentored and trained 2 postdoctoral fellows and 8 undergraduate students in microbiology research. I also wrote a clinical case for Problem Based Learning in 2007.

Service

Time devoted: 5%

Since 2007, I have served as a member on two research committees at the IUSM-NW: the Institutional Animal Care and Use Committee and the Radiation Safety Committee. Since 2008, I have reviewed 8 papers as an ad hoc reviewer for Microbiology, PNAS, Antonie van Leewenhoek, Biochemistry, PloS One, and BMC Microbiology. In 2010, I was invited to serve as a member of editorial board for the Journal of Bacteriology and Parasitology. I have served as a faculty reviewer of medical students for the IUSM Peer and Self Assessment program. In 2010, I was invited to serve as a member of graduate committee for a Ph.D student by Chosun University, S. Korea. For community service, I served as a judge for Whitney H. Young High School Science Fair in 2008. In addition, since 2010, I have served as a vice president for Korean Scientist and Engineer Association-Midwest Chapter. In this role, I organize monthly seminars for the public in an effort to promote understanding of science in the community. In 2011, I served as a reviewer for F13 Infectious disease and Microbiology Fellowship Review Panel (NIH).

Future plans

I will continue to study the molecular mechanism of SaeRS two component system. The long-term goal of this project is to develop small molecules that can inhibit the SaeRS system, and to test the efficacy of the molecules in reducing infectivity of the bacterium. Currently I am preparing an NHI RO1 grant proposal for the study, where the main research aims are 1) Molecular dissection of SaePQS ternary complex; 2). Molecular mechanism of SaeS activation by human neutrophil peptides and metal ions; 3) Determination of 3D structure of SaeS/SaeQ complex.

For the carbon catabolite repression project, we will study other aspects of *S. aureus* that are regulated by CcpA and investigate how those regulations are related to staphylococcal infection processes. I will continue the collaborative research projects to develop them into studies that can be supported by external grants. For the nanoparticle study, which is at a very early stage, Dr. Elena A. Rozhkova and I are planning to write a NIH R21grant proposal (PA-11-

149).

In teaching, since my teaching is fairly well accepted by students, I will continue my current approach. For Problem Based Learning sessions, I will incorporate more scientific concepts and methods. To keep up with current developments in medicine, I will write more cases for PBL sessions.

For service, I will continue to serve for all current responsibilities. In addition, to broaden my service area, I will actively seek to be a member of an external grant review committee for institutional organizations such as American Heart Association and National Institutes of Health.