Bioinformatics for Rational Vaccine Design and Vaccine Discovery

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One of the leading causes of death in animals, either pets or food animals, is infectious disease. Vaccines are the most effective method to prevent and control the spread of infectious disease. Bioinformatics, as a newly developed and still emerging field, incorporates a variety of scientific endeavors, including, but not limited to, the computational analysis of DNA sequence data, laboratory methods that determine the expression and cellular location of proteins, analysis of transcripts expressed at different times and under different conditions, computer analysis of genetic and amino acid sequences for prediction of protein function, and the use of computers in structure/function prediction based on comparisons of unknown and known protein structures. Recent efforts in human medicine have enrolled the use of bioinformatics to design and discover new vaccines for infectious diseases.

As an example of rational vaccine design, *Bordatella pertussis*, the causative agent of whooping cough, produces a toxin that is the principal factor involved in disease. Currently, a formalin inactivated toxoid is used for vaccination against other toxin producing pathogens, but the chemical modification is thought to alter the molecules so that some structural components that are important to the stimulation of proper cell mediated components of the immune system are either destroyed or hidden. The current vaccine used for pertussis is heat inactivated, but does have problems with side effects. Using knowledge about the amino acid sequence and which components of the sequence were important in generating protective immunity and toxicity, a group in Italy inactivated the toxin genetically using recombinant DNA methodology to convert an arginine residue at position 9 to a lysine and a glutamine at position 129 to a glycine. The detoxified molecule was demonstrated to generate cell mediated immune responses identical to the native molecule during infection.

An example of bacterial vaccine discovery is reported by another group in Italy who mined the genome of *Neiserria meningitidis*, a serious cause of bacterial meningitis. The approach was to first search the genome for open reading frames (ORFs) that encoded potential novel surface-exposed or exported proteins, using various programs including BLAST, PSI-BLAST, FASTA, MOTIFS, FINDPATTERNS, VAST, PSORT, and others. Databases such as ProDom, Pfam, and Blocks were use to predict surface-associated protein structures, such as leader peptides, trans-membrane domains, homologies to known surface proteins, etc. They were able to identify 570 ORFs encoding predicted surface expressed or exported proteins. The 570 ORFs were cloned, expressed as fusion proteins in *E. coli* and used to immunize mice. Seven of the ORFs found to be positive for three separate measures of immunity and whose genes were not predicted to be phase variable were selected for further evaluation and development.

Over the next several years the application of these approaches to veterinary pathogens is expected to expand rapidly. A review of ongoing genome sequencing projects at The Institute for Genomic Research (TIGR) shows that about 35 of the 135 microbial genome projects are animal health related organisms. It is anticipated that this number will increase as the USDA/NSF Microbial Project continues to fund at a rate of $10 million annually and the USDA-NRI adds 2-3

microbial pathogen sequencing projects. This effort is being guided by the USDA Microbial Genomics Report and Recommendations of Animal Agriculture Stakeholders, which identifies 15 additional microbes for priority sequencing and 77 others for subsequent consideration.

The use of bioinformatics for rational vaccine design and vaccine discovery fits nicely into the biological computing component of the Governor's information technology initiative. By its nature, vaccine development generates significant patent applications and licensing agreements, one of the major goals of the initiative. In addition, the function would not duplicate any current program, and would most likely be synergistic to programs in other departments involved in biological computing and bioinformatics. It is anticipated that 2 faculty and 2 research associates would be hired to bring the expertise to the School of Veterinary Medicine. It is further anticipated that the programs of several current faculty, including Dr. Phil Elser, Dr. Ron Thune, Dr. Stephen Gaunt, Dr. Gus Kousoulas, and Dr. Kathy O'Reilly, would be energized by cooperative interactions in the program.