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# FY2003 LDRD Final Annual Report Article: Pathogen Pathway Project

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FY2003 LDRD Final Annual Report Article

## **Pathogen Pathway Project**

J. Patrick Fitch and Sandra L. McCutchen-Maloney

Tracking Code: 01-SI-002

### **Project Description**

Understanding virulence mechanisms of bacterial pathogens is vital to anticipating biological threats and to improving detectors, vaccines, and treatments. This project will characterize factors responsible for virulence of *Yersinia pestis*, the causative agent of plague and a biothreat agent, which has an inducible Type III secretion virulence mechanism also found in other animal, plant, and human pathogens. Our approach relies on genomic and proteomic characterization of *Y. pestis* in addition to a bioinformatic infrastructure. Scientific and technical capabilities developed in this project can be applied to other microbes of interest. This work will establish a significant new direction for biodefense at LLNL and expand our national and international scientific collaborations.

### **Expected Results**

Results from genomic, proteomic and modeling approaches to characterize *Y. pestis* will provide a more thorough understanding of the Type III secretion virulence mechanism in general while laying the foundation for next-generation detection of biothreat agents. Several spin-off projects have resulted from this work that encompass both an applied platform for pathogen detection as well as more basic science approaches to characterize virulence mechanisms for other relevant pathogens and microbes.

### **Mission Relevance**

This project represents a national security investment that ultimately will help detect the presence of biological warfare/bioterrorist threat agents and genetically modified organisms. Our research complements existing LLNL programs in counterbioterrorism and builds on LLNL's expertise in genomics, proteomics, biocomputing, instrumentation, and national security. The project will create a functional genomics/proteomics platform that will be useful for future applications relevant to national security, environmental management, and biotechnology missions in NNSA and the DOE Office of Science.

## **Accomplishments and Results**

Work completed in FY03 includes (1) genomic and proteomic characterization of *Y. pestis*; (2) analysis of host response to *Y. pestis* exposure (3 spin-off projects); (3) characterization of *Y. pestis* regulatory proteins by SELDI-MS; (4) development of a real-time expression system to detect cascades and feedback loops that govern virulence (spin off project); (5) siRNA knockouts of virulence factors to characterize virulence and protein interactions (spin-off project); (6) development of a novel fuzzy logic-based gene network modeling approach; (7) gain of expertise in conventional pathway modeling resulting in novel biological insights for virulence; and (8) implementation of bioinformatics for data management, mining, and interpretation in genomic, proteomic, and regulatory studies.

## **People Information**

### **Foreign Nationals**

(dover2) Nir Dover ISRAEL

(palmlblad1) Magnus Palmblad SWEDEN

(forde1) Cameron Forde CANADA

### **Student Information**

(kao3) Justin Kao, Stanford University, Undergraduate

(garnham1) Janine Garnham, Rochester Institute of Technology, Graduate

## **Publications**

Forde, C.E, McCutchen-Maloney, S.L. "Characterization of Transcription Factors by Mass Spectrometry and the Role of SELDI-MS" *Mass Spectrometry Reviews* 21:419-439 (2003)

JC-150675-DR, referred publication

B.A. Chromy, A.D. Gonzales, G.A. Murphy, M.W. Choi, J.P. Fitch, S.L. McCutchen-Maloney "Proteomic Characterization of the Mechanism of Virulence in *Yersinia pestis*" 6th International Symposium on Mass Spectrometry in the Health and Life Sciences, August, 2003

JC-153609-ABS, Conference/Meeting

L.Zeller, M. Palmblad, J.P. Fitch, S.L. McCutchen Maloney "Analysis of complex biological mixtures for disease detection and prevention" 6th International Symposium on Mass Spectrometry in the Health and Life Sciences, August, 2003

JC-153512-ABS, Conference/Meeting

G.A. Murphy, J.L. Heidbrink, R.G. Langlois, J.E. Trebes, E. Dalmaso, Y. Ying, R.W. Davies, J.P. Fitch, S.L. McCutchen-Maloney "Discovery of Protein Biomarkers in Dialysis Patients Using SELDI-MS" 6th International Symposium on Mass Spectrometry in the Health and Life Sciences, August, 2003

JC-153608-ABS, Conference/Meeting

J.L. Heidbrink, G.A. Murphy, R.G. Langlois, J.E. Trebes, J.P. Fitch, E. Dalmasso, Y. Ying, R.W. Davies, S.L. McCutchen-Maloney "Discovery of Biomarkers from Dialysis Patients using ProteinChip® Technology" Users Meeting, May 4-7, 2003, Galveston, TX JC-152676-ABS, Conference/Meeting

J.P. Fitch, S.N. Gardner, T.A. Kuczmariski, S. Kurtz, R. Myers, L.L. Ott, T.R. Slezak, E.A. Vitalis, A.T. Zemla, P.M. McCready "Rapid development of nucleic acid diagnostics" Proc. IEEE 90:1708-1721  
JC-148118, Refereed publication

B.A. Sokhansanj, G.R. Rodrigue, J.P. Fitch, D.M. Wilson III "A quantitative model of human DNA base excision repair" Nucleic Acids Research 30:1817-1825  
JC-146306-PT-1, refereed publication

J.P. Fitch, B.A. Chromy, C.E. Forde, E. Garcia, S.N. Gardner, P. Gu, T.A. Kuczmariski, C. Melius, S.L. McCutchen-Maloney, F.M. Milanovich, V. L. Motin, L.L. Ott, A. Quong, J. Quong, J.M. Rocco, T. R. Slezak, B.A. Sokhansanj, E.A. Vitalis, A.T. Zemla, P.M. McCready "Biosignatures of pathogen and host" Proc. IEEE Workshop on Genomic Signal Processing and Statistics (GENSIPS)  
JC-149741, Conference/Meeting

V.L. Motin, A.M. Georgescu, J.P. Fitch, P.P. Gu, D.O. Nelson, S.L. Mabery, J.B. Garnham, B.A. Sokhansanj, L.L. Ott, M.A. Coleman, J.M. Elliott, L.M. Kegelmeyer, A.J. Wyrobeck, T.R. Slezak, E. Garcia "Temporal Global Changes in Gene Expression during Temperature Transition in Yersinia pestis" Journal of Bacteriology, accepted 2003  
JC-150715, refereed publication

Sokhansanj, B.A., Fitch, J.P., Quong, J.N., Quong, A.A."Linear fuzzy gene network models obtained from microarray data by exhaustive search" Bioinformatics, submitted 2003 JP-200201

Sokhansanj, B.A., Fitch, J.P., Quong, J.N., Quong, A.A. "Exhaustive search for fuzzy gene networks from microarray data" IEEE Engineering in Medicine and Biology Conference, 2003  
JC-154129,Conference/Meeting

B. Sokhansanj, D.M. Wilson "A Quantitative Mathematical Model of Human Base Excision Repair. II. Insights into Steady State Oxidative DNA Damage Levels and the Effects of Population Variants on Pathway Capacity" DNA Repair, submitted 2003  
JC-146306 Pt 2

Sokhansanj, B.A., Bosl, W., Quong, A.A., Quong, J.N., Fitch, J.P. "Fuzzy Rule-Based Modeling of Yersinia-Host Interactions" DIMACS Workshop on the Pathogenesis of Infectious Disease, New Brunswick, NJ  
JC-150426-ABS, Conference/Meeting

Sokhansanj, B.A., Quong, A.A., Quong, J.N., Kercher, J.R., Fitch, J.P. “Fuzzy data analysis and network reconstruction from systems biology experiments” ABRF 2003 Annual Meeting, Denver, CO  
Conference/Meeting

Sokhansanj, B.A., Wilson, D.M. “Mathematical Modeling of Human DNA Base Excision Repair” 47th Annual Meeting of the Biophysical Society, San Antonio, TX  
MI-151945, Conference/Meeting

Sokhansanj, B.A., Kercher, J.R., Quong, A.A., Quong, J.N., Fitch, J. P. “Modeling Yersnia pestis Systems Biology” 2003 ASM First Biodefense Research Meeting, Baltimore, MD, 2003  
JC-152137-ABS, Conference/Meeting

A.A. Quong, J.R. Kercher, P.M. McCready, J.N. Quong, B.A. Sokhansanj, J.P. Fitch “An indexed Modeling and experimental strategy for Biosignatures of pathogen and host”  
Journal of the Franklin Institute, in press 2003  
JC-149741rev1, Refereed publication

#### **Awards**

J.Patrick Fitch, 2002 Science and Technology Award, LLNL

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