FLORIDA INTERNATIONAL UNIVERSITY

BIOMEDICAL ENGINEERING LECTURE SERIES

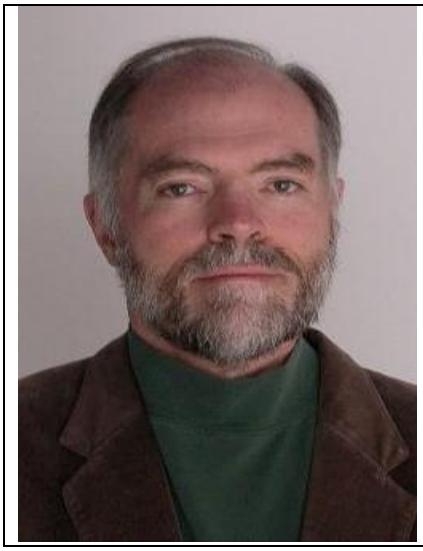
FRIDAY, MARCH 30, 2007, 10:30AM

FIU Engineering Center
10555 West Flagler Street
Room 2300

DRUG DESIGN FOR BIODEFENSE APPLICATIONS

Ionizing *Bacillus anthracis*, the etiologic source of the anthrax attacks in 2001, can be readily selected for antibiotic resistance, making the development of new antibiotics important. We have developed an extensive antibiotic discovery program that targets a variety of enzymatic pathways that are essential for bacterial growth. An overview of this program will be described, followed by a more detailed discussion of one example enzymatic target, glutamate racemase. Glutamate racemase is an essential bacterial enzyme that converts L-glutamate to the D- configuration for incorporation into the cell wall and spore capsule, but is not found in humans, and is consequently an attractive drug target for new antibiotic discovery. *B. anthracis* expresses two glutamate racemase isoforms. Computational normal mode analysis indicates that, in addition to the expected modes about the dimer site, the monomer exhibits three low frequency modes with hinge-like motions about the catalytic site. This suggests that substrate binding and product release may involve slow clamp and release actions of the two major domains of the enzyme. Molecular dynamics calculations and experimental observations suggest that Cys41, adjacent to the entrance to the catalytic site, may play a "gate-keeping" role in substrate binding. Using high-throughput (HT) screening and structure-based design, we have utilized this foundation for discovery of both active site and allosteric inhibitors. From an HTscreen of approximately 100,000 compounds, we have discovered an allosteric inhibitor that appears likely to act via binding to a region of the enzyme that prevents its release of D-Glu, locking it into the product-bound conformation. Using structure-based design, we have also designed substrate analogs that exhibit enhanced inhibitory activity. The details of this discovery process will be discussed.

MICHAEL E. JOHNSON, PHD



Dr. Michael Johnson is currently Professor and Director of the Center for Pharmaceutical Biotechnology and Associate Director of the Center for Structural Biology at the University of Illinois at Chicago. He received his M.Sc. in physics from Northwestern University in 1970, and a Ph.D. in physics with specialization in biophysics from Northwestern University in 1973.He moved up the ranks at UIC, becoming Professor in 1984. At UIC, he also served as Associate Dean for Research and Education in the College of Pharmacy from 1986-1991, and as Acting Head of Medicinal Chemistry & Pharmacognosy from 2000-2001. He was named an Established Investigator of the American Heart Association in 1979, received the American Association of Colleges of Pharmacy Paul Dawson Biotechnology Award in 2004, was named a University of Illinois Scholar in 2004, and has served on a variety of NIH and NSF review and advisory panels. He has been Principal Investigator of numerous NIH and foundation grants, is currently Program Director for two NIH program project-type grants totaling approximately $5 million/yr, and has published approximately 100 peer reviewed article, edited a biotechnology textbook, and has received multiple patents.

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