



PRESS RELEASE

CONTACT: Tara A. Ellis
716-898-8596

FOR RELEASE: Friday, October 12, 2007

**FIRST HIGH-RES 3-D STRUCTURES OF MAMMALIAN HSP90 PROTEIN SOLVED,
KEY TO BETTER TARGETS FOR AIDS, SEPSIS, CANCER DRUGS**
HWI Scientist Dr. Dan Gewirth's Groundbreaking Research Makes Cover of Molecular Cell

Dr. Dan Gewirth, Hauptman-Woodward senior research scientist, has just solved the structure of the first mammalian GRP94 protein implicated in immune diseases such as sepsis, AIDS and certain cancers. His work is being published today in a cover article in a top scientific journal - *Molecular Cell*.

Gewirth's study confirms his 2001 hypothesis that this protein – GRP94 – is from the same family as the better known HSP90 proteins. As ligand-regulated chaperones – proteins that help other cellular proteins achieve their active shapes, the HSP90s are key players in cellular regulation and recognition. The HSP90 proteins have been the subject of increasing international interest as scientists have discovered that they can be targeted therapeutically with drugs that lead to either stimulation as well as inhibition. For example, inhibitors of HSP90s are being developed as therapies for diseases ranging from cancer to sepsis, and drugs that stimulate HSP90 action may be appropriate therapies for diseases involving protein folding, such as cystic fibrosis, prion diseases, and Alzheimer's Disease.

Since 2001, Gewirth and his lab have been using the technique of X-ray diffraction to solve the first high-resolution structure of this protein from mammalian origins, to understand its function and to determine if it is indeed a member of the HSP90 family of proteins. The structure and activity patterns of this protein prove conclusively that this is indeed a member of the same family.

“Our work opens the door to a more intensive evaluation of this protein both from a mechanistic as well as a therapeutic point of view. In addition to aiding our understanding of the fundamental biology of chaperone-mediated protein folding, this work lays the foundation for the design of drugs that specifically target individual members of the hsp90 family” Gewirth, who also holds a post as an associate professor in the Structural Biology department of the University at Buffalo which is housed at the Hauptman-Woodward Medical Research Institute, said.

Why Is This Important?

This is groundbreaking work for a number of reasons: It is the first high resolution picture of any member of the hsp90 family. High resolution is needed for a detailed understanding of protein function. It is also the first structure of a mammalian member of the hsp90 family. This is important since drugs and other therapeutics need to be developed for human use, and thus must target the mammalian protein. Finally, the work shows for the first time how members of the hsp90 family of chaperone proteins can differ from each other, while still being part of the same overall family.

Scientific Understanding – The mammalian member of this protein family is different than those previously studied which were solved from either bacteria or yeast. Human energy production and consumption rates are more similar to those found in the GRP94 proteins than to the more widely studied HSP90 proteins. This means that the insights gained by a greater scientific understanding of how GRP94 works will have more direct applications to human diseases.

2/2/2/2/2/2

Hauptman-Woodward's Gewirth Published in *Molecular Cell*

Medical Implications and Drug Development – Inhibitors currently are being designed for HSP90 in an attempt to treat the diseases in which HSP90 plays a role. However, these are broad-spectrum inhibitors of all HSP90s which means that unwanted side effects may occur. The Gewirth lab's work clarifies GRP94's place in this family and has already stimulated interest in this chaperone as a drug target. This understanding would allow for the long-term development of a family of drugs that could be narrowly targeted for individual proteins, for example specifically treating sepsis only.

Economic Impact – Just as companies have been founded to develop HSP90 inhibitors, the same potential exists here. "This will spur a new line of inquiry into GRP94. While this work is its infancy, medicinal chemists will be interested in developing GRP94-targeted drugs," Gewirth said.

Other authors of the publication include: D.Eric Dollins, recent Ph.D. graduate from Duke University, Joshua J. Warren, post-doctoral fellow at Duke University and Robert M. Immorrino, recent Ph.D. graduate from Duke University.

About Gewirth

In addition to his position as an HWI senior research scientist, Gewirth is an associate professor of Structural Biology at the University at Buffalo. Prior to joining HWI in 2005, Gewirth was an assistant professor in the Department of Biochemistry at Duke University. He completed post-doctoral research at both Yale and Harvard, received his Ph.D. from Yale University in 1988 and his bachelor's degree from the University of Chicago in 1982. Gewirth's research is focused primarily on structural studies of HSP90 chaperones, drug design, protein folding; nuclear hormone receptors; and basal transcription factors. Gewirth and his wife live in Buffalo.

About HWI

With more than 50 years of exceptional scientific research, HWI is an independent, non-profit facility specializing in the area of fundamental biomedical research known as structural biology. Hauptman-Woodward's team of more than 75 staff members is committed to improving human health by studying the causes of diseases, as well as potential therapies, at their basic molecular level. HWI is located in the heart of the Buffalo Niagara Medical Campus in downtown Buffalo, New York, in a new state-of-the-art structural biology research center at 700 Ellicott Street. For more information, visit HWI's website at www.hwi.buffalo.edu or call 716-898-8600.