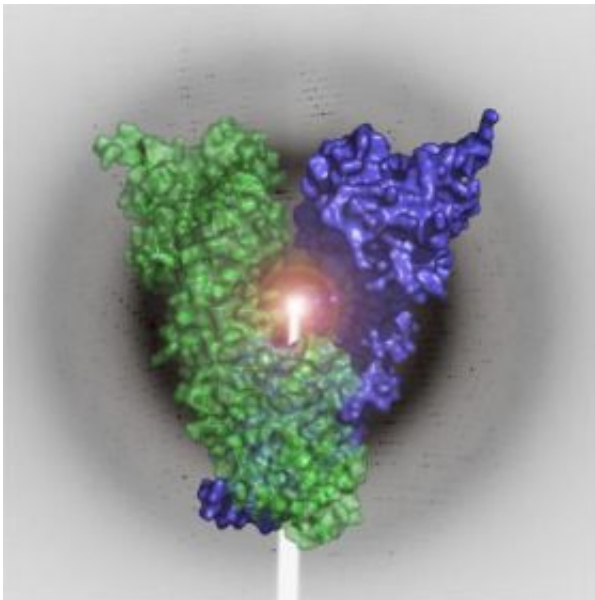


# First high-res 3D structures of mammalian HSP90 protein solved

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HWI Scientist Dr. Dan Gewirth's Groundbreaking Research Makes Cover of *Molecular Cell*. Credit: Dan Gewirth

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.

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.

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.

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.

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.

Source: Hauptman-Woodward Medical Research Institute

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