Pacific Researchers Discover Potential Drug Treatment to

# Prevent a Rare Form of Heart Failure

## eureka moment

It was one of those moments of discovery every researcher hopes for. And for Thomas J. Long School of Pharmacy and Health Sciences Professor Mamoun Alhamadsheh, it was a climactic moment after five years of research seeking the veritable "needle in a haystack."

While completing a post-doctoral fellowship at Stanford University, Alhamadsheh and co-researchers used highly specialized equipment to screen 130,000 drug molecules down to 200 identified as having strong potential. Joining the Pacific faculty in 2011, Alhamadsheh and his Pacific research team conducted tests on those 200 molecules, pinpointing one that may provide a cure for a rare, inherited form of heart failure.

"I couldn't believe it!" said Alhamadsheh of the moment when student researcher Sravan Penchala '15 showed him the startling results. "I had to repeat it personally, going through each step carefully to be sure."

**"It was the happiest moment of my life," said Penchala, a third-year doctoral student and research assistant with Alhamadsheh. "It was a dream come true for me to be involved in this type of groundbreaking research."**

This breakthrough could lead to the first drug therapy to prevent FAC, or familial amyloid cardiomyopathy. The disease is caused by a genetic mutation that destabilizes Transthyretin (TTR), a protein synthesized by the liver and secreted into the blood. The destabilized TTR causes abnormal deposits of insoluble proteins called amyloid in the heart tissue, eventually resulting in heart failure. FAC affects nearly 4% of African Americans and about 10 to 20 percent of adults 65 and older.

Currently, the only approved treatment for FAC is a combination of liver and heart transplants, which are extremely costly, risky and difficult to obtain. There is no FDA approved preventative treatment.

**"Conceivably, in three to four years, individuals could be genetically screened for the disease and could begin taking this drug treatment so they would never get FAC"**

**— Professor Mamoun Alhamadsheh**

Penchala was the first author on the research paper that documented their success with the chemical, called AG-10. The paper was published in the Proceedings of the National Academy of Sciences of the United States of America in June. Alhamadsheh is the lead researcher on the project.

**"I never imagined I would be able to be first author on a paper in this publication," said Penchala. "It's usually for people with many more years of research."**

In addition to Penchala, Alhamadsheh's research team at the School of Pharmacy and Health Sciences includes grad student Yu Wang '13 and professors Miki S. Park and William K. Chan, along with Dr. Isabella Graef at the Stanford School of Medicine. Researchers at Scripps Research Institute in San Diego also contributed to earlier phases of the research.

AG-10 is a small molecule drug that effectively stabilized mutant TTR when tested multiple times in blood samples. Initial testing has also shown AG-10 to be nontoxic in small animals, paving the way for pre-clinical evaluation.

The next step in a path to a potential cure is to secure funding. It could take upwards of $5 million to get the drug through the phases of animal and human testing required for FDA approval. Since no one has made progress on a treatment for this disease, the FDA has approved a process to expedite the testing of this drug.

"Conceivably, in three to four years, individuals could be genetically screened for the disease and could begin taking this drug treatment so they would never get FAC," said Alhamadsheh.

And the impact of this research could reach even beyond those suffering from FAC. Alhamadsheh and his team are also seeing some indications that there is a potential for the AG-10 drug to provide a preventative treatment for other related diseases.

**"It has been suggested that TTR plays a protective role against Alzheimer's disease and, with further research, we hope that our studies could provide tools to prevent Alzheimer's disease."**

"In addition to FAC, this discovery could potentially help patients who suffer from other forms of TTR diseases that affect the peripheral nervous system," said Alhamadsheh. "It has been suggested that TTR plays a protective role against Alzheimer's disease and, with further research, we hope that our studies could provide tools to prevent Alzheimer's disease."

Read more in the study published in the Proceedings of the National Academy of Sciences at www.PNAS.org/content/110/24/9992.

*— By Sheri Grimes*