MedicalXpress

From Bench to Bedside: Insect Research Yields Promising New Drug for Diabetes, Hypertension and Inflammatory Disorders

March 5 2009

(PhysOrg.com) -- A new drug developed at the University of California, Davis, to treat diabetes, hypertension and inflammatory diseases has entered Phase IIa of human clinical trials to evaluate its efficacy.

The winding, twisting path that took entomology professor Bruce Hammock from his lab, to collaborative research with other UC Davis scientists, to the founding of a $50 million investment biotechnology company, to clinical trials proved as steep as the mountains he loves to climb.

The compound, a soluble epoxide hydrolase enzyme (s-EH) inhibitor called AR9281, is “a first-in-class drug, which may treat a suite of major cardiovascular and metabolic diseases,” said Hammock, who with UC Berkeley cell biologist Sarjeet Gill discovered the enzyme in 1969 while researching fundamental insect biology.

“This is one of the few examples of basic research in an academic laboratory moving through target validation and compound optimization all the way to the clinic,” he said.

Tracing the events that led to the discovery of the enzyme, Hammock recalled doing research at UC Berkeley four decades ago with then-colleague Sarjeet Gill. Gill discovered the enzyme in mammals. Shortly after, Hammock found the novel enzyme in insects.

“Both of us have been chipping away at this problem ever since,” Hammock said. “By 1975 we were convinced that this was a therapeutic target but no one else was. When we finally found potent inhibitors for the enzyme that worked in whole animals, we had a tool to demonstrate that this was a promising therapeutic target.”

Hammock was initially interested in regulating the development of insect larvae. With the discovery of the enzyme inhibitor, however, he switched part of his research from “pest control to pain control.”

The enzyme is involved in the metabolism of arachidonic acid, a key signaling molecule implicated in diabetes, hypertension (high blood pressure) and inflammatory disorders. “It’s an enzyme in the same arachidonic biochemical pathway where many other common pharmaceuticals such as aspirin, Advil, Aleve, ibuprofen, Motrin and others are active,” he said.

The Phase I trial evaluated the safety, safe dosage range and side effects of the drug candidate. It then entered Phase IIa to test its efficacy.

UC Davis physicians and scientists praised the new drug as promising.

Nephrologist and cell biologist Robert Weiss of the UC Davis Health System said the drug could lead to important health implications for patients with type 2 diabetes, a chronic disease affecting an estimated 23.6 million children and adults in the United States.

Cardiologist and cell biologist Nipavan Chiamvimonvat of the UC Davis Health System, a longtime collaborator with Hammock, said many diseases tend to occur together in vascular biology. “So, a compound that addresses heart failure, as we have shown, combined with the reduction of blood pressure, inflammation and diabetes is very attractive.”

Last year, the researchers showed that the compounds reduced atherosclerosis is obese mice.

The Phase IIa clinical trial is a double-blind, placebo-controlled study. Officials will enroll a total of 150 patients with impaired glucose tolerance, mild obesity and mild to moderate hypertension.

Each patient will receive 28 days of treatment. The AR9281 enzyme inhibitor will be studied for safety, tolerability, reduction of blood pressure and various measures of glucose and lipid metabolism. Results are expected the first quarter of 2010.

At the onset, Hammock faced two major obstacles: financing and moving the drug into clinical trials.

“Finding resources in an academic laboratory to move a first-in-class drug through clinical trials, is difficult,” Hammock said. “It costs $700 million to $1.2 billion to get a treatment to the market.”

“Publicly funded research,” the professor said, “results in many new possible pharmaceutical targets that could be exploited by either small molecule drugs or biotechnology. However, society faces a serious problem in that few of these leads are followed and there is a widely held view that universities cannot validate a target, much less optimize a pharmaceutical.”

So in 2002, Hammock founded the biotech company Arête Therapeutics Inc. www.aretetherapeutics.com/, naming the company with a mountaineering term that means “sharp, steep ridge.” Specifically, the company is named for the arêtes of the Bear Creek Spire of the Sierra Nevada that Hammock, his sons and occasionally other UC Davis faculty and students climb.

“I founded the company because I failed to transfer technology to the public from the University of California by other means in the past,” Hammock said. “And I received nothing more than a passing interest from pharmaceutical companies at that time, but now they are very interested.”

In 2003, he and his son, also named Bruce, incorporated the company to move the materials into clinical trials.

“To get funding we had to make a case for a new drug when current therapy was thought to be adequate,” the professor said. “There are few good drugs for end organ failure and vascular inflammation.” Vascular inflammation is involved in diabetes and obesity side effects.

“The collaborative and interdisciplinary environment at UC Davis permitted us, with support from the National Institute of Environmental Health Sciences, to optimize the potency and drug properties of the s-EH inhibitors to the stage where we could present a convincing picture to venture groups of compounds ready to move to the clinic.”

In 2005, the company raised more than $51 million in Series A financing led by Frazier Healthcare Ventures, Alta Partners, Three Arch Partners, Burrill & Company and Altitude Life Science Ventures.

Today, the biotech company, based in Hayward, is dedicated to the discovery and development of novel drugs to treat type 2 diabetes, hypertension and inflammatory disorders, Hammock said.

“Our main goal,” Hammock said, “was to set up a system of a science-driven company where we reduce the cost of drug registration by using very good incisive science. We also want to reward and motivate the people who do the work; provide a funding and training environment to help teach students and postgraduates to write proposals; and allow

scientists to move between an academic and industrial environment in the early stage to help determine career directions."

Another goal: a low-cost, affordable drug. "The sickest people in the world, of course, cannot pay for the drugs they need," Hammock said. "The chemistry developed around the s-EH inhibitors allows us to make powerful but inexpensive drugs that could be produced in developing countries."

Meanwhile, the clinical trials under way represent two firsts, said James Sabry, president and chief executive officer of Arête Therapeutics. "This is the first clinical study of a s-EH inhibitor in patients, and the first study designed to establish proof of concept that s-EH inhibition modulates glucose metabolism or blood pressure in patients with impaired glucose tolerance and hypertension."

"The compound looks quite promising and it's an example of how basic work in insect biology led to a $50 million company — by far the largest Series A financing of an early stage drug in many years — and a drug in Phase II human clinical trials," Hammock said. "This all shows the value of basic research and what we can do to help humanity."

Hammock, who joined the UC Davis Department of Entomology faculty in 1980, holds a joint appointment in cancer research with the UC Davis Medical Center and directs the National Institute of Environmental Health Sciences (NIEHS) Superfund Program on the UC Davis campus, as well as the National Institutes of Health (NIH) Training Program in Biotechnology, and the NIEHS Combined Analytical Laboratory.

Elected to the prestigious National Academy of Sciences in 1999, he received the UC Davis Faculty Research Lecture Award in 2001 and the Distinguishing Teaching Award for Graduate and Professional Teaching in 2008.

Provided by UC Davis