

Scientists explore whether what heals the head can also heal the heart

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What do heart disease and dementia have in common? Perhaps more than meets the eye, according to researchers at the University of Rochester Medical Center.

A diverse group of scientists – experts in cardiology, neurology, immunology, microbiology and chemistry – are teaming up to study drugs that show promise in the treatment of [dementia](#) for the treatment of an equally debilitating disease – [heart failure](#). In this case, the connection between the head and the heart lies in a particular enzyme that they believe plays a role in the development of both conditions.

The team, headed by Burns C. Blaxall, Ph.D., Harris A. "Handy" Gelbard, M.D., Ph.D., and Stephen Dewhurst, Ph.D., recently won the largest grant awarded to date by the University's Clinical and Translational Science Institute (CTSI) – \$250,000 over two years. The grant, part of the CTSI's newly initiated Incubator Program, is larger than most awarded by the Medical Center.

Thomas Pearson, M.D., Ph.D., who heads the CTSI and helped develop the new program, says tremendous weight was given to forming new teams that had never worked together before, and for these teams to study things they had never addressed before. The Blaxall/Gelbard/Dewhurst team fit the bill on both counts.

"The brain and the heart are two completely different systems that are rarely considered to have biological, or emotional, overlap," said Blaxall,

lead researcher for the new study and an associate professor within the Aab Cardiovascular Research Institute at the Medical Center. "We may find that they are not so different after all."

The unique investigation stems from years of research by Gelbard, a neurologist, and Dewhurst, a microbiologist and immunologist, to develop the world's first treatment designed to prevent dementia commonly associated with HIV infection. They have already created a compound that shows great promise in the laboratory and works by blocking an enzyme known as MLK3, which plays a key role in the inflammatory process.

In patients with HIV-associated dementia, excess inflammation – a byproduct of the body's natural attempt to protect itself from the virus – damages healthy brain cells and leads to cognitive difficulties. Excess inflammation is also a hallmark of heart failure: Tissue damage from a heart attack, for example, ignites an inflammatory response to guide repair, but if the response is too strong, "inflammation overload" leads to scarring that hinders the heart's ability to pump blood throughout the body.

Given Gelbard and Dewhurst's understanding of MLK3, and Blaxall's expertise in the molecular mechanisms underlying heart failure, they joined forces to study if the enzyme plays a role in the disease. According to Gelbard, who heads the Center for Neural Development and Disease at the Medical Center, "This is a great example of how one area of research can really help inform another."

Their preliminary studies of cardiac cells suggest that, in fact, MLK3 is involved in the inflammation and scarring characteristic of heart failure. Even more exciting is research showing that a compound very similar to the MLK3 inhibitor in development for HIV-associated dementia slowed the progression of heart failure.

The Rochester team is working in close collaboration with Val S. Goodfellow, Ph.D., CEO of biotechnology company Califia Bio Inc., in the ongoing identification and development of a range of MLK3 inhibitor compounds.

"The idea that MLK3 inhibitors could have an impact in treating dementia, but also in treating heart failure, bridges very prevalent, very bad diseases that we need better treatments for," noted Randy N. Rosier, M.D., Ph.D., co-director of the Pilot and Collaborative Studies Key Function within the CTSI who, along with fellow co-director Richard T. Moxley, M.D., selected the Blaxall/Gelbard/Dewhurst team to receive the Incubator grant. "We are extremely enthusiastic about this collaboration and think it has great potential to bring in additional funding from outside the University and birth even bigger, longstanding research programs here."

In addition to attracting new funding, the Incubator Program represents an important investment in the University's future by involving students and young investigators in the translational research process. Blaxall's team, which also includes Sanjay B. Maggirwar, Ph.D., will mentor four trainees as part of the grant.

The study comes at a time when the general model for drug discovery and development is changing. As pharmaceutical companies reduce their investments in early-stage research, due to high costs and substantial risk, academic institutions like the [Medical Center](#) are playing an increasingly larger role.

According to Dewhurst, chair of the Department of Microbiology and Immunology, "Companies are looking to academia to come up with novel ideas and to test and "de-risk" them at an early phase and a lower cost." With the support of the CTSI, through the Incubator grant and a host of other funding programs, researchers at Rochester are poised and

ready to take the reins.

As for the current research, Gelbard says that while HIV-associated dementia is a very important problem, and one that he's focused his entire career on, it is still a small part of the health care universe. "If our work ultimately leads to a potential therapy for heart failure the implications of that are far larger. That would be a wonderful piece of serendipity."

Provided by University of Rochester Medical Center

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