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\$1.2 Million Grant for Further Development of Compstatin, A Drug to Halt an Overzealous Immune System

(Philadelphia, PA) -- In some ways, the body's first line of defense can also be its worst enemy. The complement system is a series of biochemical reactions that activate in response to foreign molecules and is an important part of the immune system.

Unfortunately, when it is activated at the wrong time, complement is also responsible for organ transplant rejection and a long list of diseases.

Researchers at the University of Pennsylvania Medical Center have found a way to control complement with Compstatin, a small molecule that blocks the reactions involved in a complement response. The National Institute for General Medical Sciences (NIGMS) has awarded John D. Lambris, PhD, a professor in the Department of Pathology & Laboratory Medicine, a \$1.2 million grant to continue the development of Compstatin into an effective drug.

"Among the compounds we have studied, I believe Compstatin holds real promise," said Lambris. "Until Compstatin, most complement inhibitors were either only marginally effective or actually toxic to humans." Part of the reason it has been so difficult to control complement is because of the complex nature of the human immune system. Complement proteins serve as a passive alarm system, watching for pathogens that may enter the blood system. When a complement protein finds something it does not recognize, it attaches itself to the invader, summoning the full wrath of the immune system, which attempts to destroy the invader. Complement is not a simple sequence of reactions either, but a series of interlocking cascades, or chain reactions, of biochemical events involving at least 30 proteins.

"Fortunately, there is a point where all the protein cascades intersect," said Lambris. "We figured that if we can stop the cascade at this point, we can halt the reaction regardless of what pathway started it."

Lambris and his colleagues focused on one particular complement protein, an enormous molecule called C3. They created billions of protein fragments and searched for ones that might bind to the C3 protein and inactivate it. Amazingly, they found a ring-shaped protein, made up of 11 amino acids, which, despite its relatively small size, inactivated C3 entirely. Lambris named the molecule Compstatin.

"Since C3 was so large, we assumed that we would find many different fragments that would bind to C3, and from them we would learn more about the important functional parts of the molecule," said Lambris. "Instead, out of all the possibilities we find the one fragment that attaches directly to C3 and disables it."

Compstatin owes its effectiveness -- and potential use as a therapeutic -- to its small size. Compstatin's ring structure makes it resistant to proteases, enzymes that destroy proteins, so it is less likely to be broken down before it meets its target. Smaller molecules like Compstatin are also more readily adaptable to use as an oral medication.

Lambris and his colleagues have already demonstrated Compstatin's abilities in the laboratory, and the NIGMS grant makes further exploration possible.

"Compstatin has great potential as a complement inhibitor," said Mark Tykocinski, MD, Chair of Penn's Department of Pathology and Laboratory Medicine. "Developing complement inhibitors with therapeutic potential has been a long-standing goal of medical science, and such agents could contribute significantly to the treatment of an array of human diseases." Although the complement proteins are part of the immune system, they do not always limit themselves to potentially disease-causing invaders-- complement does not discriminate between bacteria and transplanted organs or even implanted surgical devices. Complement can also attack healthy tissue, and a variety of diseases are associated with complement gone awry, such as multiple sclerosis and hemolytic anemia. In addition, complement is thought to play a role in the destruction of cells during strokes, heart attacks, and burn injuries.

The University of Pennsylvania Health System is distinguished not only by its historical significance --first hospital (1751), first medical school (1765), first university teaching hospital (1874), first fully integrated academic health system (1993) --but by its position as a major player on the world stage of medicine in the 21st century. Penn ranks second among all American medical schools that receive funds from the National Institutes of Health, perhaps the single most important barometer of research strength.

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