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**NEW 'KAMIKAZE' CHEMICALS SHOW
PROMISE FOR BLOCKING ENZYMES THAT
CAUSE BLOOD CLOTTING AND EMPHYSEMA**

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Dubbed "suicide inhibitors" because they target specific enzymes and then self-destruct, a new breed of pharmaceuticals may someday help prevent blood clots, emphysema, organ transplant rejection and skin blistering.

Chemists at the Georgia Institute of Technology have already created a substance that prevents blood clotting in laboratory animals, demonstrating rapid "on/off" properties. Known as ACITIC, the substance is probably inappropriate for human therapy, but scientists expect that another suicide inhibitor from the same class of compounds can be refined to control bleeding during surgery, or to prevent heart attacks, strokes, and other circulatory disorders caused by blood clots.

At the same time, chemist Dr. James C. Powers believes his work, funded by the National Institutes of Health, could provide new information about the serine protease family of enzymes which attack proteins within the body, sometimes causing problems such as emphysema.

Like all suicide inhibitors, ACITIC is programmed to self-destruct after attracting a specific enzyme -- in this case, a clotting factor called thrombin. Since it resembles an amino acid that is naturally attracted to thrombin, ACITIC lures the enzyme onto a hook-like portion of its structure and then "explodes." In this way, ACITIC prevents clotting in rabbits.

"ACITIC is like a bomb inside a package tied with a ribbon," Powers explained. "Thrombin comes along and pulls this ribbon and the bomb explodes, killing thrombin."

Thrombin is one of many serine protease enzymes which attack proteins at various sites within the body. In the stomach, for example, these enzymes assist digestion by degrading proteins in food. They also play a role in fertilization and fighting infection.

But enzymes can create havoc, too. Some people suffer from emphysema because their bodies don't produce a protease inhibitor which prevents enzymes from destroying proteins in the lungs. Unchecked by an inhibitor, the enzymes begin to destroy lung linings. (Smoking cigarettes can also damage the inhibitors and cause emphysema, Powers noted.)

Other protease enzymes cause organ transplant rejection and skin blistering. "ACITIC might not be ideal for anti-clotting, but that doesn't mean we can't find another use for it," Powers said. "There are literally a dozen potential uses for inhibitors of these proteases."

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In animal studies performed at Emory University's Department of Surgery, ACITIC prevented clotting within five minutes of infusion into rabbits, and it stopped working two minutes after dosage was discontinued, said Dr. David N. Ku, a surgeon for both schools.

Existing anti-coagulant drugs, heparin and warfarin, work slowly and therefore can create problems for surgeons, or for patients susceptible to blood clots. "Cardiovascular disease is the leading cause of death in this country," said Dr. Steve W. Oweida, an Emory University vascular surgeon. "The need for a new anti-coagulant is clear."

Sixty to 90 minutes after the last drop of heparin has been administered, the drug may still prevent clotting, and this can result in excessive bleeding. Since it is a biological product derived from the lining of pig intestines, heparin may also cause certain auto-immune responses. Warfarin, a compound from the coumarin class of substances found in grass, doesn't stop working for three days.

Known by the chemical name "7-amino-4-chloro-3-(3-isothiureidopropoxy)isocoumarin," ACITIC is one of the compounds in the class of isocoumarins. Although they are chemical 'cousins' to the coumarin class, isocoumarins are structurally distinct and demonstrate promising advantages for anti-clotting therapy. Further, Ku said, isocoumarin derivatives like ACITIC could potentially be prescribed in pill form to prevent clots in high-flow, arterial regions; heparin can only be administered into the skin or vascular system via hypodermic needle, and it is generally ineffective on platelet-rich arterial clots.

Powers and research scientist Dr. C.M. Kam at Georgia Tech developed the patented isocoumarin substitute ACITIC (and 17 other derivatives) using a five-step synthesis process. An understanding of the clotting process guided the development of ACITIC.

Whenever a wound occurs, inactive enzymes receive a signal to take action, and they serve as catalysts, activating many additional clotting factors. This process is repeated in a rapid cascade of reactions which ultimately prompt thousands of thrombin enzymes to proliferate at the site of the wound and attack fibrinogen, a protein. By chopping the polypeptide "tail" from fibrinogen, thrombin produces a fiber-shaped protein that becomes aligned in a mat or blood clot. ACITIC halts clotting by destroying thrombin, Powers said.

Animal studies were performed only after the effectiveness of ACITIC was measured in the laboratory. First, rabbits were anesthetized as required by federal regulations. Next, ACITIC was administered and anti-clotting effects were calculated. To further test ACITIC, clotting was induced in 10 rabbits; a control group didn't develop clots after receiving ACITIC, Ku said. Increased dosages produced comparably more effective anti-coagulation, he added. ACITIC is probably toxic to humans, Powers said, but he believes a similar substance can be refined. The research was published in Biochemistry, and papers have also been prepared for Thrombosis Research and Hemostasis.

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