

Key found to breakthrough drug for clot victims

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A team of researchers at Oregon Health & Science University and Washington University in St. Louis have described for the first time the mechanism that gives a mutant enzyme molecule that they have engineered – and patented – the potential to become a breakthrough drug for treating heart attacks and strokes.

The team described how their genetically modified enzyme, called WE-thrombin, functions as a potent clot busting agent while retaining little of the power that thrombin, its non-engineered parent, has to cause the opposite result, a cascade of clot building. They did so in a paper published recently in *Arteriosclerosis, Thrombosis, and Vascular Biology* (ATVB), a peer-reviewed journal of the American Heart Association. An editorial commentary in ATVB hailed this breakthrough as “a significant advance in understanding the functions and antithrombotic potential of (WE thrombin) in particular, and the approach of using engineered human proteins more broadly...”

“The successful development of WE-thrombin would be a major medical breakthrough in antithrombotic therapy, ultimately saving thousands of lives worldwide each year,” said the lead investigator András Gruber, M.D., Ph.D., associate professor of medicine in the division of hematology and medical oncology, OHSU School of Medicine.

Thrombin is an enzyme that, paradoxically, has the capacity both to promote and prevent blood clotting. Balancing the two depends on a

highly complex system of positive and negative feedback loops. Normal blood clotting is vital to minimize bleeding in the event of an injury. Excessive clotting can lead to thrombosis, the blockage of a blood vessel.

Heart attacks and strokes – most often the result of blood clots – remain two of the three leading causes of death and severe disability in the United States. The toll from these diseases persists at high levels in part because the drugs now relied on to stop or break up clots – such as heparin or TPA, tissue plasminogen activator – pose the risk of triggering hard-to-control systemic bleeding. Also, they can't be injected outside of a clinical setting in patients that present with symptoms of stroke or heart attack and, even then, only after time consuming preliminary diagnostic tests and scans. Every minute that treatment is delayed after the onset of a stroke or heart attack reduces the odds of survival or recovery.

The researchers contemplate that, if it is approved for use in humans, WE thrombin – which the research team has demonstrated is effective and safe in large primates – could safely be injected by paramedics or others, whenever someone displays the first symptoms and signs of a stroke or heart attack without fear of causing harm if the symptoms prove to be a false alarm.

Aronora LLC, a startup biotechnology company, has been formed by Gruber along with the primary co-investigators and others, to seek financial support for preclinical and early clinical development of WE-thrombin as a safe alternative to existing antithrombotic drugs. The market for such drugs is estimated to exceed \$20 billion per year worldwide. The patents on WE-thrombin are currently co-owned by the investigators' parent institutions, OHSU, Emory University and Washington University.

“WE-thrombin is the most potent antithrombotic agent that ever has

been described,” said Gruber. “And that’s because of its specificity. It effectively utilizes a natural “drug delivery system” of circulating blood platelets and white blood cells that accumulate in the clot formation process to deliver its punch directly to a blood clot. The process parallels that of targeted drug delivery. It’s effective inside a blood vessel, but not at all effective outside the blood stream, which is exactly what you want from an antithrombotic agent.”

“What we’ve done recently,” added coinvestigator Owen J.T. McCarty, Ph.D., “is located the exact point where the catalytic reaction takes place in vivo that makes this molecule work as a superior antithrombotic agent.” McCarty, an expert in platelet biology, is assistant professor of biomedical engineering in the department of cell and developmental biology, OHSU School of Medicine.

Blood platelets are small cells that sense an injury and rush to form a clot to reduce bleeding. They do so by binding thrombin, which cuts fibrinogen into strands of fibrin to form the “glue” of a clot. The process becomes self sustaining, or autocatalytic, which means that the glue is produced and reproduced in a rapid chain reaction. Thrombin subsequently counterbalances the process by activating protein C inside the blood vessel, which shuts down the autocatalytic reaction in the blood stream.

WE-thrombin, the mutant form of thrombin, lacks the ability to create the glue but still can produce activated protein C (APC) inside the blood vessels, which makes it a unique, locally acting anticoagulant. The molecule enhances this ability, the research team discovered, by attaching itself to a receptor, or sticking point, called glycoprotein Ib (GPIb), located on the surface of platelets. In doing so, WE-thrombin shoulders aside – and thus inhibits – the protein (the von Willebrand factor) that promotes coagulation, which now has to compete for the same receptor on the platelets.

Because of WE-thrombin's specificity and potency, the dosage required to be effective in humans, Gruber said, is expected to be less than 0.5 milligrams, and possibly less than 0.1 milligrams, or 200- to 1,000-fold less than the dosage levels of TPA commonly being administered now in heart attack and stroke.

Source: Oregon Health & Science University

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