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New molecule could be key to anti-heart attack drug

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When too many blood platelets stick together in the bloodstream, they form dangerous clots that can clog blood vessels and cause a heart attack. If a clot doesn't get dissolved or rapidly removed, it can cause permanent damage or even death. But new research by Rockefeller University scientists suggests that it should be possible to create a clot-busting pill that targets a receptor on the blood cells' surface, something that high-risk patients could take at the first sign of chest pain.

Platelets are the blood's search and rescue team, rushing to the site of an injury and sticking together to help prevent excessive bleeding. Unfortunately, when they perform the same activity in a narrowed artery with atherosclerosis, they can produce a dangerous clot. A few powerful medications exist that can completely prevent them from sticking together, but doctors must administer the drugs intravenously. With a pill, patients could keep it in their medicine cabinets, saving precious time and preventing excess damage.

The key to such a pill, the Rockefeller scientists say, is a receptor called αIIbβ3 on the platelets' surface that is intimately involved in the aggregation process. Interfering with αIIbβ3 can prevent an unwanted clot or "thrombus," and the three αIIbβ3 inhibitors currently on the market can do just that. But they also have side effects and risks. Barry Coller, David Rockefeller Professor and head of the Allen and Frances Adler Laboratory of Blood and Vascular Biology, and laboratory manager Robert Blue have found a new molecule, called RUC-1, that not only appears to sidestep these problems but, unlike existing drugs, could

be taken orally.

The αIIbβ3 receptor is made up of two halves: the αIIb subunit and the β3 subunit. Previous attempts to create αIIbβ3 inhibitors that could be taken orally led to drugs that bind to both halves; this blocks other platelets from attaching, but also changes the configuration of the receptor to its "on" position. Once the drug wears off, the inhibitor may leave the receptor in the on position, making the platelet primed and ready for other passing platelets to bind. "As a result, once the inhibitor is gone and the receptors are still in the active conformation, you get a paradoxical increase in thrombus formation," Blue says.

In research published in Blood, Coller and Blue and their colleagues Marketa Jirouskova and Marta Murcia describe the structural effects of RUC-1, which was discovered by screening more than 33,000 compounds in collaboration with Charles Karan at the university's High Throughput Screening facility. Rather than binding to the entire receptor, RUC-1 binds to only half of it, αIIb, presumably leaving the other half in the off position. This structural effect appears to have practical implications. In a separate study, together with collaborators at Children's Hospital of Philadelphia, Blue and Coller are now assessing the effect of RUC-1 on mice with human αIIb and mouse β3 receptors.

Their research is some of the first to be supported by the new National Institutes of Health Clinical and Translational Science Award. Research assistant Amanda Harrington is now working to synthesize more potent derivatives of the molecule. And at the same time, the scientists are screening the 250,000 compounds in the NIH Small Molecule Repository using the robotic systems at Columbia University to search for molecules that could be even more effective than RUC-1.

"RUC-1 could provide advantages over the currently available inhibitors," Blue says. If someone was at very high risk for having a

heart attack, he could keep the drug on hand and take it the same way doctors currently suggest using aspirin, swallowing the pill at the first sign of chest pain. “This would be the same idea, only much more potent,” he says.

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