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Penn Study Shows Way to Make Treatment of Rare Blood Disorder More Affordable and Effective

PHILADELPHIA — A **University of Pennsylvania** research team has defined a possible new way to fight a disease that is currently treatable only with the most expensive drug available for sale in the United States. In a study published this month in *Blood*, the Penn team describes the strategy, based on the oldest part of the human immune system – called "complement" -- that could turn out to be less costly and more effective for the majority of patients with a rare blood disorder.

Complement is a network of more than 50 proteins in the blood and on cell surfaces that quietly cruise the body, keeping a low profile until triggered into action. On the other hand, this system can turn, contributing to a broad spectrum of immune, inflammatory, and age-related diseases.

John Lambris, PhD, the Dr. Ralph and Sallie Weaver Professor of Research Medicine in the Department of Pathology and Laboratory Medicine in the **Perelman School of Medicine**, studies this early-warning system and how to correct it when its response goes overboard.

This is known to be the case with paroxysmal nocturnal hemoglobinuria (PNH), a rare but life-threatening hematological disorder, which is estimated to affect between 1 and 5 per million people. In PNH, defective expression of regulatory proteins on the surface of blood cells leaves them vulnerable to complement attack. This can lead to premature death of the red blood cells, a process called hemolysis, which clinically results in severe anemia and contributes to a high risk of clotting.

Lambris and **Daniel Ricklin, PhD**, research assistant professor of Pathology and Laboratory Medicine, are developing novel therapeutics to tame this inappropriate complement activation and protect cell surfaces from attack.

Eculizumab (Soliris, an Alexion Pharmaceuticals drug) -- to date the only approved therapeutic for PNH -- reduces hemolysis and gives relief from blood transfusions for most PNH patients. However, Eculizumab is costly (currently the most expensive drug used in the US at more than $400,000 per year per patient), and one third of PNH patients continue to require blood transfusions to manage their anemia. As first described by co-author Antonio Risitano, MD, at the University of Naples in Italy, this non-response is due to fragments of complement C3 proteins on the surface of their red blood cells, which are eventually attacked by immune cells.

Lambris and colleagues have thought that inhibition of the "complement cascade" at the level of C3 proteins using small inhibitory molecules might be a superior strategy as it prevents both hemolysis and immune cell recognition while being potentially more cost-effective when compared to the current antibody-based treatment.

The team investigated the effect of a C3 inhibitor called Cp40 and its long-acting form PEG-Cp40 on self attack and resulting hemolysis using human PNH cells. Both compounds demonstrated inhibition of hemolysis and efficiently prevented deposition of C3 fragments on PNH red blood cells. In non-human primates, a single injection of PEG-Cp40 into the blood stream resulted in a longer time that the drug stayed in circulation, a property important for drug development.

"We think these two compounds are excellent and potentially cost-effective candidates for further clinical

investigation," says Lambris, who hopes that the compounds could be tested in clinical trials by 2015.

Editor's Note: Lambris and Ricklin are the inventors of patents and/or patent applications owned by Penn that describe the use of complement inhibitors for therapeutic purposes. Lambris is a founder and equity holder of Amyndas Pharmaceuticals, which has exclusively licensed the Cp40 and PEG-Cp40 technologies from Penn and is developing complement inhibitors for clinical applications.

Other authors from Penn include Robert A. DeAngelis, Zhuoer Lin, Yijun Huang, and Edimara S. Reis.

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