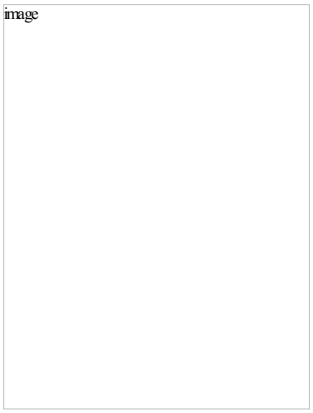

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Expanding complement therapeutics for the treatment of paroxysmal nocturnal hemoglobinuria

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Abstract (185 words)

Paroxysmal nocturnal hemoglobinuria (PNH) is widely regarded as an archetypal complement-mediated disorder that has propelled complement drug discovery in recent decades. Its pathology is driven by chronic complement dysregulation resulting from the lack of the GPI-linked regulators DAF and CD59 on susceptible erythrocytes. This complement imbalance fuels persistent C3 activation on affected erythrocytes, which culminates in chronic complement-mediated intravascular hemolysis. The clinical application of eculizumab, a humanized anti-C5 antibody that blocks terminal pathway activation, has led to drastic improvement of therapeutic outcomes but has also unveiled hitherto elusive pathogenic mechanisms that are now known to contribute to the clinical burden of a significant proportion of PNH patients. These emerging clinical needs have sparked a true resurgence of complement therapeutics that offer the promise of even more effective, disease-tailored therapies for PNH. Here we review the current state of complement therapeutics with a focus on the clinical development of C3-targeted and alternative pathway-directed drug candidates for the treatment of PNH. We also discuss the relative advantages and benefits offered by each complement-targeting approach, including translational considerations that might leverage a more comprehensive clinical intervention for PNH.