

Complement Backgrounder

Complement is part of the body's immune system that destroys foreign organisms (e.g. bacteria) as well as whole cells (self or foreign). Since Alexion's founding in 1992, the company's research efforts have focused primarily on complement inhibition – the selective blocking of the complement cascade. In 2007, Alexion became the first company in the United States to discover, develop and successfully commercialize a terminal complement inhibitor – Soliris® (eculizumab).

Complement Biology

The human immune system can respond to foreign organisms such as bacteria and viruses in two different ways: by making antibodies that bind to such invaders in the blood, thus marking them for destruction by white blood cells, or, by employing specific complement proteins that are already in the blood to mark and attack these foreign particles.

In the presence of foreign particles, complement proteins become activated and bind to the surface of these particles. This triggers a cascade, or chain reaction, among complement proteins, with one protein leading directly to the creation of the next one in the complement cascade. Complement proteins then form holes or pores in the invading organisms, causing their destruction. Complement proteins can also mark foreign particles so that white blood cells can remove them.

While complement is essential to maintaining health, it can also destroy healthy cells and tissue. To prevent this, the body normally produces a range of specialized complement inhibitors to protect itself. In complement-inhibitor-deficiency diseases, including paroxysmal nocturnal hemoglobinuria (PNH), patients lack certain naturally occurring complement inhibitors. In other complement-mediated disorders, healthy tissue is attacked when complement is activated inappropriately or excessively.

Complement Inhibition

The complement inhibition technology of Soliris is a groundbreaking therapeutic approach that has the potential to treat patients with a variety of diseases that involve complement activation. The inhibition of complement in animal models has been shown to reduce laboratory measures of kidney disease,¹ asthma,² transplantation,^{3,4} multifocal motor neuropathy,^{5,6} myasthenia gravis,⁷ lupus,¹ and arthritis.⁸

The complement protein known as C5 acts at a relatively late stage in the complement cascade and when activated, is directly involved in activating host cells, attracting immune cells that can cause inflammation, and destroying cells by triggering pore formation. If C5 activity is not regulated properly, the resulting complement activity may result in one of many human disorders.

In the development of Soliris, researchers at Alexion identified complement protein C5 as the best place to block the complement cascade, so that the normal disease-preventing functions of complement largely remain intact, while the activity of C5 that leads to inflammation and cell destruction is blocked.

More information about PNH and complement inhibition is available at <http://www.pnhsource.com>.

References

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