Expanding horizons in the complement pathway

The complement pathway's intricate network of proteins, which have a key role in the innate immune system, are attracting dealmakers' attention as targets for a variety of inflammatory diseases.

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BioPharma Dealmakers

The complement pathway is a regulated cascade of proteins that supports or complements (hence the name) the activity of antibodies and phagocytes in clearing infections. The pathway comprises three strands known as the classical pathway, the lectin pathway and the alternative pathway (**Fig. 1**), which converge on complement protein C5 and eventually lead to the formation of a membrane attack complex that lyses target cells. However, inappropriate or unregulated activation of the pathway is involved in various inflammatory diseases, making it an attractive drug target.

The pioneering successes of therapeutics that modulate the complement pathway have been developed for rare diseases such as paroxysmal nocturnal hemoglobinuria (PNH), in which blood cells are lysed by inappropriate complement pathway activity. In 2007, the US Food and Drug Administration (FDA) approved the first therapeutic that specifically targeted the complement pathway: Soliris (eculizumab), which is marketed by Alexion Pharmaceuticals for the treatment of PNH. Since then Soliris—which is a monoclonal antibody that inhibits C5—has been approved for the treatment of several other rare diseases, including atypical hemolytic uremic syndrome (aHUS) in 2011, generalized myasthenia gravis in 2017 and neuromyelitis optica spectrum disorder in June this year (**Fig. 1**).

Alexion Pharmaceuticals has also developed a long-acting C5 inhibitor, Ultomiris (ravulizumab), which gained its first approval by the FDA for the treatment of PNH in December 2018. In addition, plasma-purified and recombinant preparations of C1 esterase inhibitor (C1-INH), which modulates the complement pathway as well as other pathways, have been approved for the treatment of hereditary angioedema (HAE), also known as C1-INH deficiency. The recombinant C1 esterase inhibitor product Cinryze (marketed by Shire Pharmaceuticals) was approved by the FDA in 2008 and gained a label expansion for pediatric patients with HAE in 2018.

Encouraged by this success, drug developers have begun to explore further opportunities to target particular proteins and pathways within the complement cascade, including factor D, C3 and C6 amongst others. Over the past decade, the field has expanded rapidly and today more than 50 candidates are in clinical development for a range of indications from age-related macular degeneration (AMD), to autoimmune anemias and kidney disorders.

Pathway to partnering

The development of such a large pipeline of candidates has triggered a significant amount of partnering activity between biopharma companies in the field. A selection of these recent partnering deals targeting the complement pathway is illustrated in Figure 1.

The majority of deals and approvals in Figure 1 are focused around the component C5, reflecting its pivotal position in the cascade. In October 2019, UCB Pharma acquired the complement-focused company Ra Pharma and its lead candidate zilucoplan, a peptidic C5 inhibitor, in a $2.1 billion cash deal. The once-daily, self administered zilucoplan is currently in phase 3 trials for the treatment of generalized myasthenia gravis. Results are expected in early 2021. Regeneron Pharmaceuticals has also targeted C5, penning a $1 billion deal with Alnylam Pharmaceuticals in April 2019 on a range of RNA interference (RNAi) therapeutics, including a combination of a small interfering RNA (siRNA) therapy with an anti-C5 antibody for C5-mediated diseases.

Other components in the pathway have been the focus of deals too. One of the pioneering companies in the field with its two FDA-approved products, Alexion Pharmaceuticals, has also been involved in a number of partnering deals (**Fig. 1**). In October this year, the company acquired Achillion Pharmaceuticals in a deal worth $930 million upfront. The deal brings together Alexion's portfolio targeting C5 with Achillion's factor D inhibitors targeting the alternative pathway. Achillion's lead candidate, danicopan, is an oral factor D inhibitor that is expected to enter phase 3 trials in 2020, and its second-generation inhibitor ACH-5228 has entered clinical development. Alexion also partnered with Complement Pharma in 2018 to develop its preclinical candidate CP-010, a monoclonal antibody that targets C6, for neurodegenerative disorders. Alexion could pay up to €14 million in milestones through phase 1b development, and also has the option to acquire Complement Pharma. In a third deal signed in March this year, Alexion will pay $25 million upfront to Zealand Pharma to develop peptides for up to four complement pathway targets. Zealand Pharma will handle the preclinical development of the drug candidates, and Alexion will take over from the investigational new drug filing stage. Alexion could pay Zealand Pharma $25 million for exclusive rights to the first candidate and over $600 million in development and sales-related milestones.

And finally, two deals shown in Figure 1 focus on the component C3. Apellis Pharmaceuticals and SFJ Pharmaceuticals announced a deal in February 2019 to develop APL-2, a pegylated cyclic peptide inhibitor of C3 for several indications, including PNH, coronary artery disease and warm autoimmune hemolytic anemia. This deal could be worth up to $250 million to Apellis, including $120 million in upfront and near-term milestone payments. In the second deal, Catalyst Biosciences and Mosaic Biosciences partnered in 2017 to develop intravitreal anti-C3 therapies that target dry AMD and other retinal diseases.

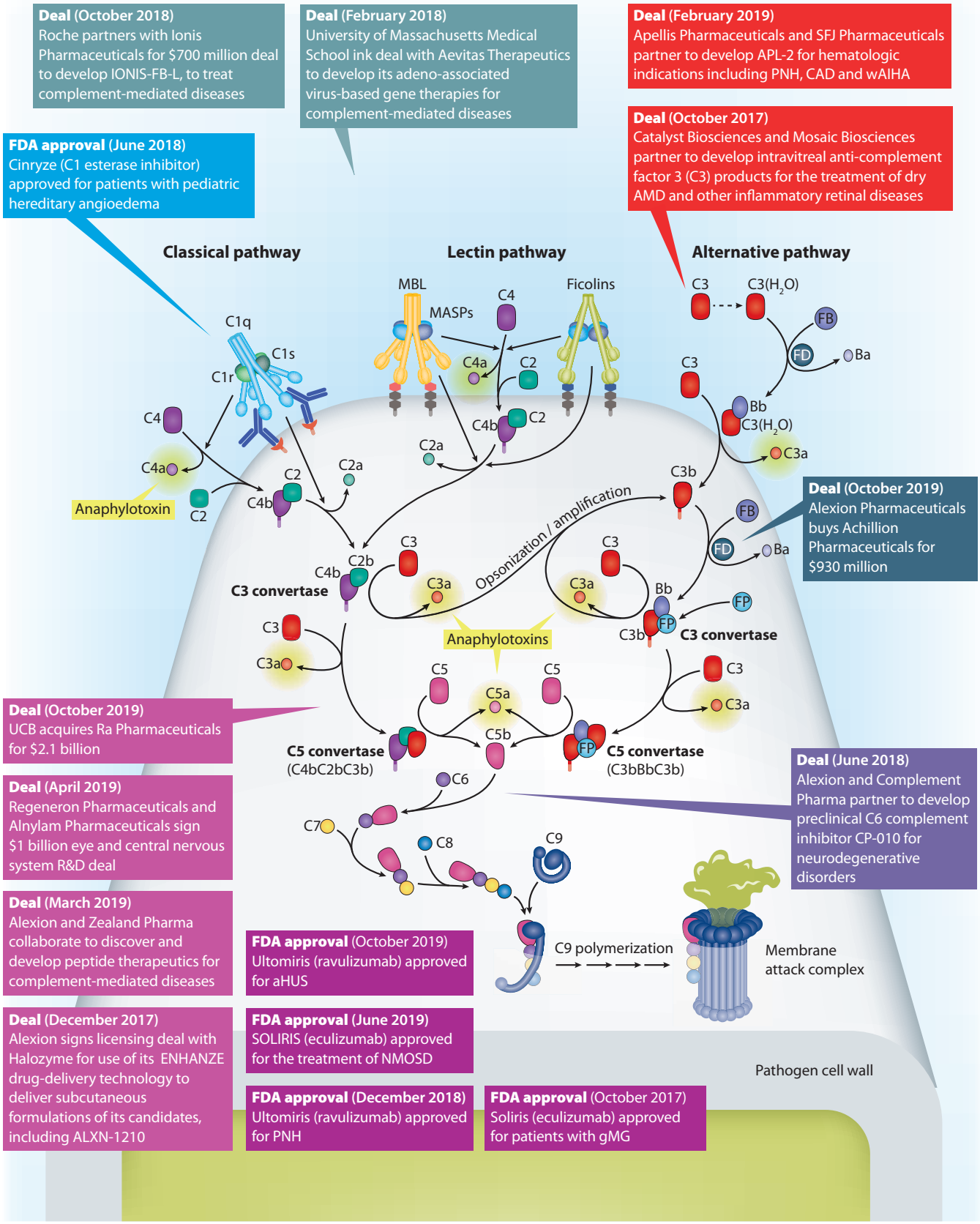

Fig. 1 | Partnering and approvals in the complement pathway. The pathway consists of three strands, known as the classical pathway, the lectin pathway and the alternative pathway, which culminate in the formation of a membrane attack complex that kills target cells directly. Selected deals and approvals since 2017 are highlighted. aHUS, atypical hemolytic uremic syndrome; AMD, age-related macular degeneration; CAD, coronary artery disease; gMG, generalized myasthenia gravis, MASP, MBL-associated serine protease; MBL, mannos-binding lectin; PNH, paroxysmal nocturnal hemoglobinuria; NMOSD, neuromyelitis optica spectrum disorder; wAIHA, warm autoimmune hemolytic anemia.