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Empasiprubart Proposed Mechanism of Action

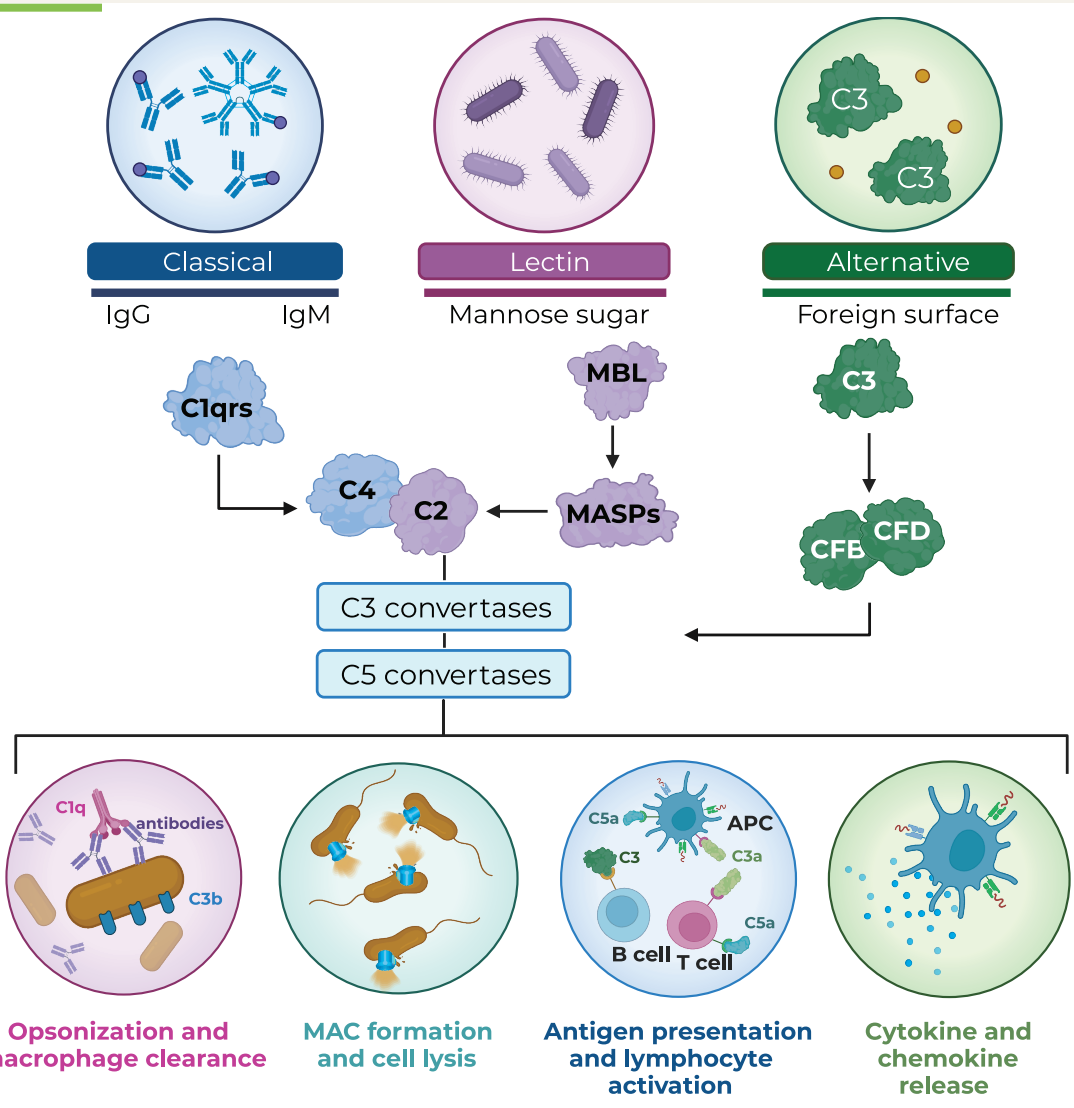
The role of complement in immunity

- The complement system includes more than 30 soluble and membrane-bound proteins that promote the phagocytosis and lysis of pathogens by cells of the innate immune system[1-3]
- The 3 complement pathways (classical, lectin, and alternative) are activated by distinct triggers such as antigen-antibody complexes, microbial carbohydrates, or spontaneous surface activation[2]
- Activation leads to a signaling cascade of enzymatic reactions that triggers physiological responses in innate and adaptive immunity, including[1]:

Innate responses
- Opsonization of antigens[1,2]
- MAC formation and cellular lysis[1]

Adaptive responses
- Antigen presentation and activation of lymphocytes[1,2]
- Cytokine release to tune the direction and extent of immune activation[2]

The complement system is composed of 3 activation pathways triggered by pathogens or antibodies bound to antigens[1,2,4,5]



The complement system plays an important role in host defense but also contributes to the pathophysiology of numerous diseases when dysregulated[5]

Empasiprubart is an investigational agent that is not approved for use in any indication by the FDA as efficacy and safety have not been established.

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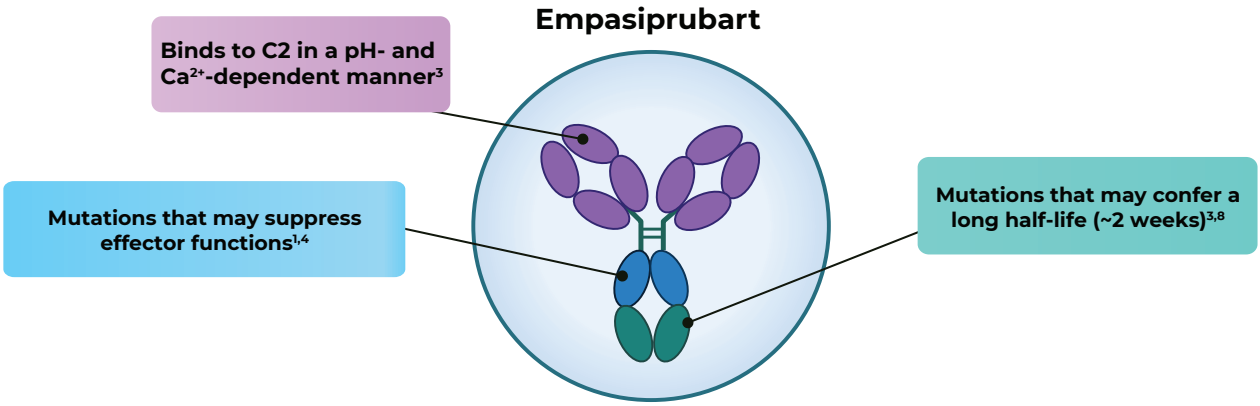
Empasiprubart Proposed Mechanism of Action

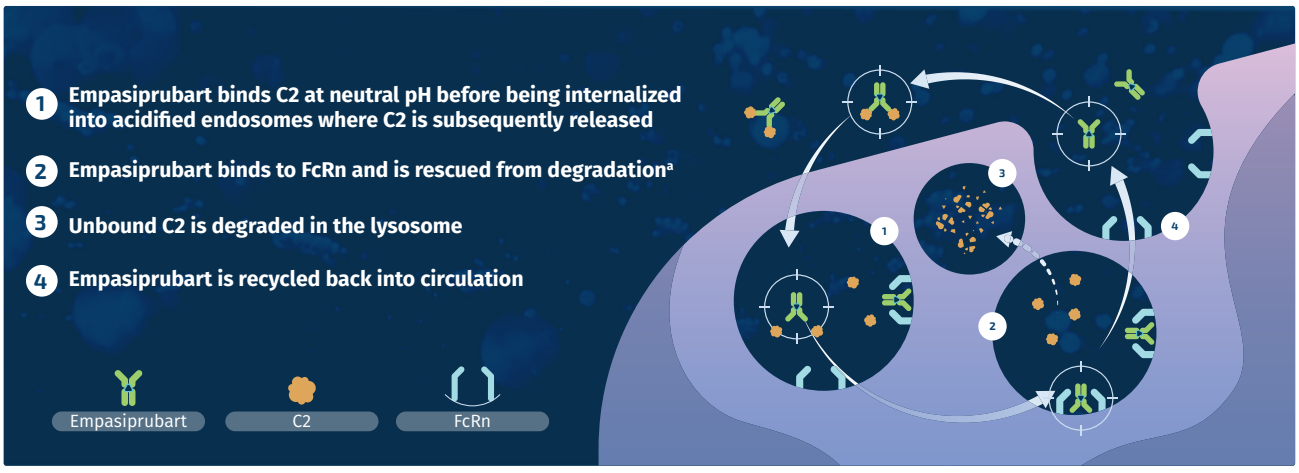
Empasiprubart is an investigational humanized IgG1 complement-inhibiting antibody targeting C2 to selectively block classical and lectin pathway activation[3,6]



Binding C2 represents an investigational approach for modulating complement-mediated autoimmune diseases[3]

- C2 is upstream of C3 and C5. Targeting C2 blocks downstream activation of both the classical and lectin complement pathways. This dual pathway inhibition leaves the alternative pathway intact for the antimicrobial function of complement[1,3,4]
- C2 in plasma is less abundant than other complement factors. Most other complement factors are present in serum at higher concentrations with more rapid turnover, necessitating higher doses or more frequent administration of inhibitors for therapeutic effect[3,9-11]
- Patients with genetic deficiencies in C2 display a less severe phenotype than those with deficiencies in other complement components[3,4,12]

Proposed interaction of empasiprubart with C2[3]



[a]Empasiprubart has increased affinity for FcRn at acidic pH and therefore remains bound to FcRn, which may prolong half-life[3,8]

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Figures 1 and 2 were created with BioRender.com

Abbreviations:
APC, antigen presenting cell; C, complement component; CF, complement factor; Fc, fragment crystallizable region; FcRn, neonatal Fc receptor; Ig, immunoglobulin; MAC, membrane attack complex; MASP, mannose-binding lectin serine protease; MBL, mannose-binding lectin.

References
1. Sarma JV, Ward PA. *Cell Tissue Res*. 2011;343(1):227-235. **2.** Murphy K. Janeway's Immunobiology. 8th ed. Garland Science; 2012. **3.** Van de Walle I, et al. *J Allergy Clin Immunol*. 2021;147(4):1420-1429 e7. **4.** Garred P, et al. *Pharmacol Rev*. 2021;73(2):792-827. **5.** West EE, et al. *Lancet*. 2024;403(10424):392-405. **6.** Budding K, et al. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(1). **7.** Hezareh M, et al. *J Virol*. 2001;75(24):12161-12168. **8.** Vaccaro C et al. *Proc Natl Acad Sci*. 2006;103(49):18709-18714. **9.** Tange CE, et al. *Clin Chem Lab Med*. 2018;56(9):1498-1506. **10.** Kasperska-Zajac A, et al. *J Inflamm*. 2013;10(1):22. **11.** Galindo-Izquierdo M, Pablos Alvarez JL. *Cells*. 2021;10(1). doi:10.3390/cells10010148 **12.** Coss SL, et al. *J Autoimmun*. 2023;137:102979.