TEHRAN UNIVERSITY OF MEDICAL SCIENCES

Immunotherapeutic Drugs for the Treatment of Immune-Mediated Glomerular Diseases

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REVIEW

Clinical advances in immunotherapy for immune-mediated glomerular diseases

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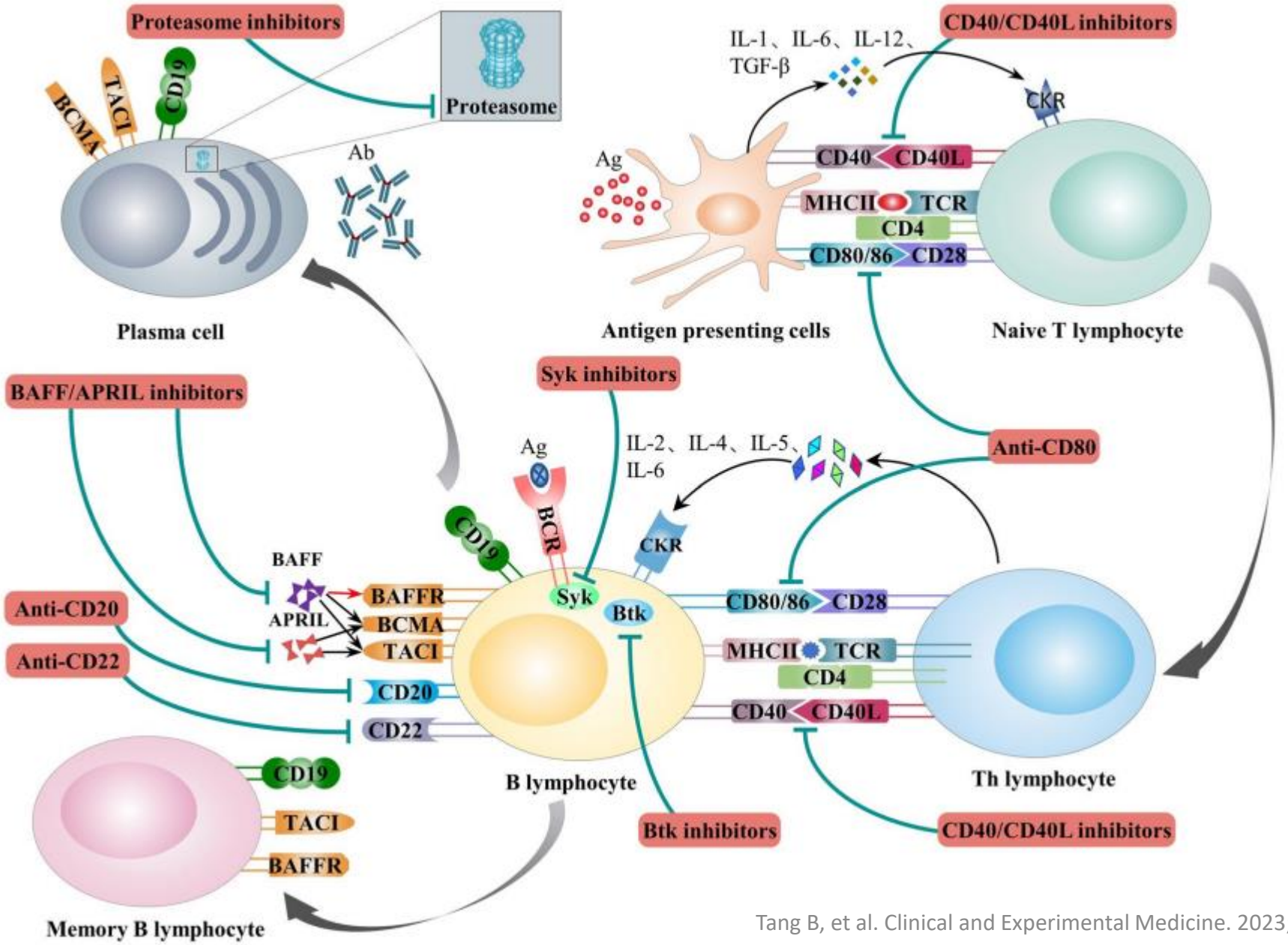
Immune Response Process and Targets of Immunotherapies in T/B Cells and APCs



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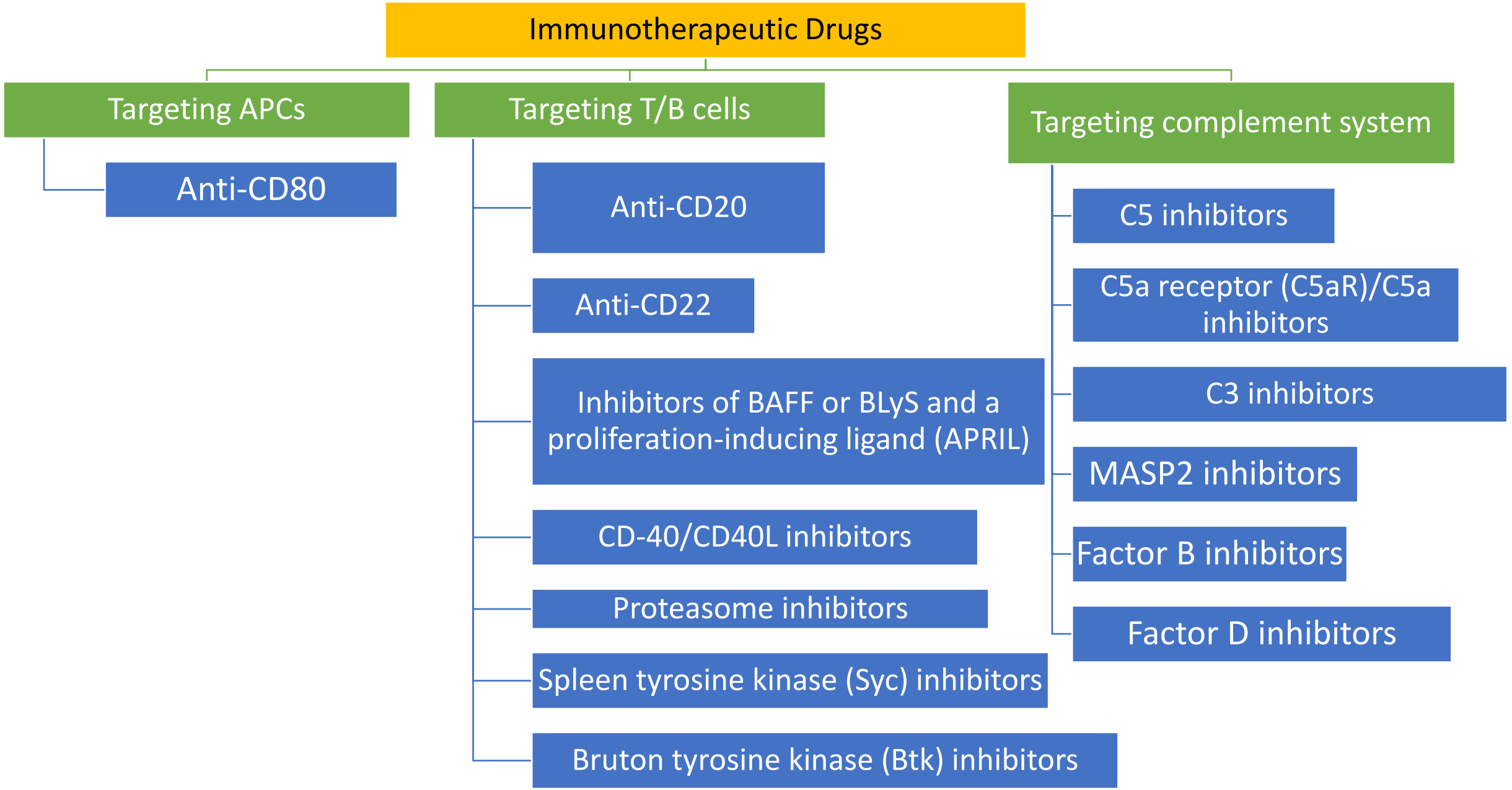

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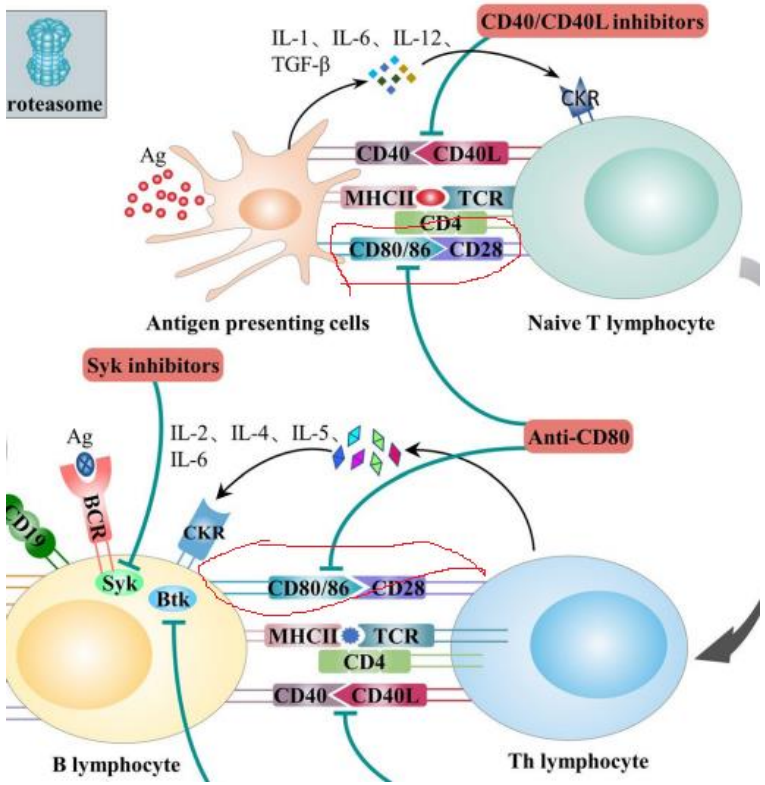
Immunotherapies Targeting APCs: Anti-CD80

- On APCs, CD80 binds to the receptor CD28 on T cells, providing signal for T cell activation. CD80 can also bind to the receptor cytotoxic T-lymphocyte associated protein 4 (CTLA-4) on T cells, limiting T-cell activation and proliferation.
- Abatacept, a recombinant fusion protein targeting CD80, consists of the extracellular structural domain of human CTLA4 and part of the Fc structural domain of human IgG1. This CTLA4 Ig competes with CD28 to bind CD80/86 on the APC surface, inhibiting T-cell activation and T-cell dependent B-cell activation.
- Abatacept decreases various cytokines (TNF-α, IL-2, IL-4, IL-5, IL-6, and IFN-γ).
- Abatacept can also inhibit the formation of T follicular helper cells and induce the transformation of naive T cells into Tregs.



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Abatacept

- FDA approved for aGVHD prophylaxis, RA, psoriatic arthritis.
- Prefilled syringe 50mg/0.4ml; 87.5mg/0.7ml; 125mg/1ml.
- Phase 1/2 RCTs in LN on Abatacept in combination with GC± mycophenolate or cyclophosphamide did not reach primary outcomes. Only more decrease in proteinuria or dsDNA level were seen. Need for more studies.
- Successful case series in FSGS. Needs for results of RCTs.

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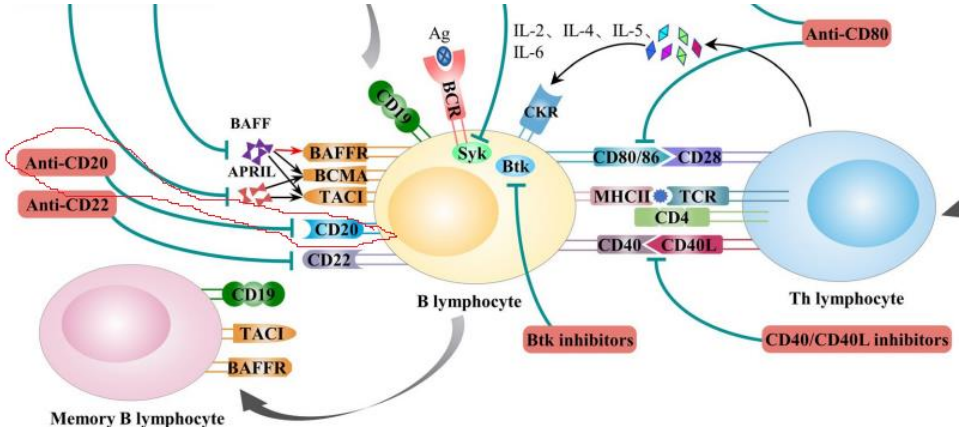
Lexicomp. 2024

Immunotherapies Targeting T/B Cells: Anti-CD20

- CD20 is expressed on the surface of most B cells from pre-B lymphocytes onwards, but is absent in plasma mother cells and plasma cells.
- CD20 deficiency can decrease the number of circulating memory B cells, antibody class switching, and IgG levels.
- Anti-CD20 depletes B cells through various mechanisms, including antibody dependent cellular cytotoxicity, antibody-dependent cell-mediated phagocytosis, and complement dependent cytotoxicity.



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KDIGO 2021

Immunotherapies Targeting T/B Cells: Anti-CD20

- Rituximab has been recommended/suggested by KDIGO for MN, AAV and LN.
- More evidence is needed for using in the treatment of FSGS, MCD, and IgAN.
- Due to the rarity of anti-GBM disease, there is no RCT to verify the therapeutic effect of anti-CD20 antibodies. Some case reports and small retrospective studies have reported that rituximab has effect.
- Newer generation that are humanized: ocrelizumab, ofatumumab, obinutuzumab.
- No comparative study between rituximab and new generation anti-CD20 in glomerular disease.

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KDIGO 2021

Obinutuzumab

- Obinutuzumab, a humanized anti-CD20 monoclonal antibody, has a greater affinity for the Fcγ receptor on effector cells than rituximab, and more depleting B cells effect.

- Approved for CLL, some types of lymphoma.
- Intravenous solution 1000mg/40mL. IV.

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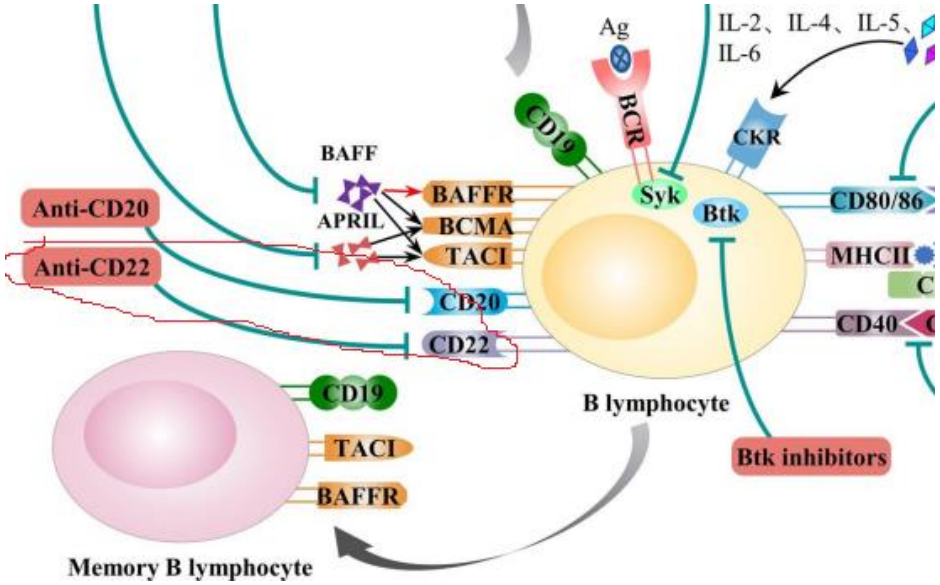
Ofatumumab

- Approved for CLL and relapsing multiple sclerosis
- Concentrated solution 100mg/5mL, Auto-injector 20mg/0.4mL
- IV

Uptodate 2024

Immunotherapies Targeting T/B Cells: Anti-CD22

- CD22 is a transmembrane glycoprotein belonging to the immunoglobulin superfamily.
- It is specifically expressed in B lymphocytes.
- The expression level of CD22 varies during the development of B lymphocytes.
- Becomes highly expressed in mature B cells. Eventually, it is absent on the surface of plasma mother cells and plasma cells.
- As the coreceptor of BCR, CD22 plays a key role in the development and survival of B cells and is a crucial component of humoral immune system regulation.



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Epratuzumab

- Is a humanized anti-CD22 mAB that downregulates BCR signaling by binding to CD22, leading to cell death.
- It also downregulates CD19, CD79β, and CD21 on the B-cell surface and further reducing the BCR signal.
- Moreover, it inhibits the production of pro-inflammatory cytokines (TNF and IL-6) without affecting the production of anti-inflammatory cytokines (e.g., IL-10).
- Under investigation for treatment of SLE and LN.

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Immunotherapies Targeting T/B Cells: Inhibitors of BAFF and a Proliferation-Inducing Ligand (APRIL)

Both BAFF and APRIL are members of TNF superfamily.

BAFF is also known as B lymphocyte-stimulating factor (BLyS).

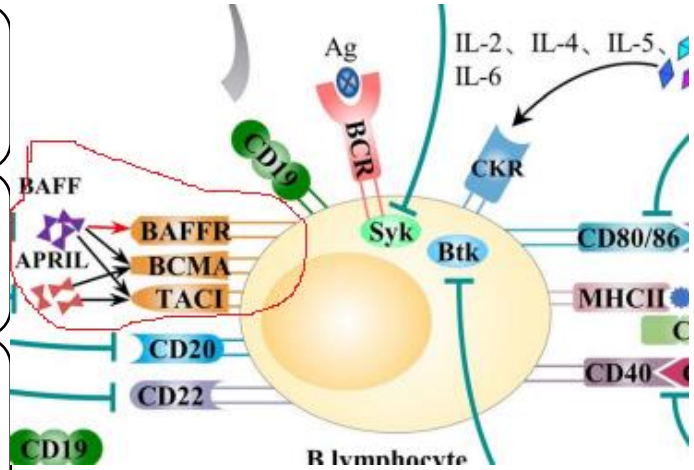
BAFF and APRIL share two receptors, namely, transmembrane activator and cyclophilin ligand interactor (TACI) and B-cell maturation antigen (BCMA).

Furthermore, BAFF can bind to B-cell activating factor receptor (BAFFR).

BAFF is mainly produced by neutrophils, monocytes, and macrophages. It plays significant roles in B-cell survival, differentiation, maturation, antibody production and class switching.

In addition to its effect on B cells, studies have shown that BAFF can promote T cell activation, proliferation, and differentiation.

BAFF and APRIL are overexpressed in some autoimmune diseases, such as SLE, suggesting their potential involvement in the pathogenesis of these diseases.



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Immunotherapies Targeting T/B Cells: Inhibitors of BAFF and APRIL

- Belimumab, a monoclonal antibody targeting BAFF, has been approved by FDA and EMA for treatment of SLE and LN.
- Prefilled syringes 200mg/ml (1ml), Solution reconstituted 120mg, 400mg. IV, SC.
- Belimumab is under investigation for MN, IgAN, and AAVs.
- Another BAFF/APRIL inhibitor is atacicept, a chimeric recombinant fusion protein under RCT for SLE.

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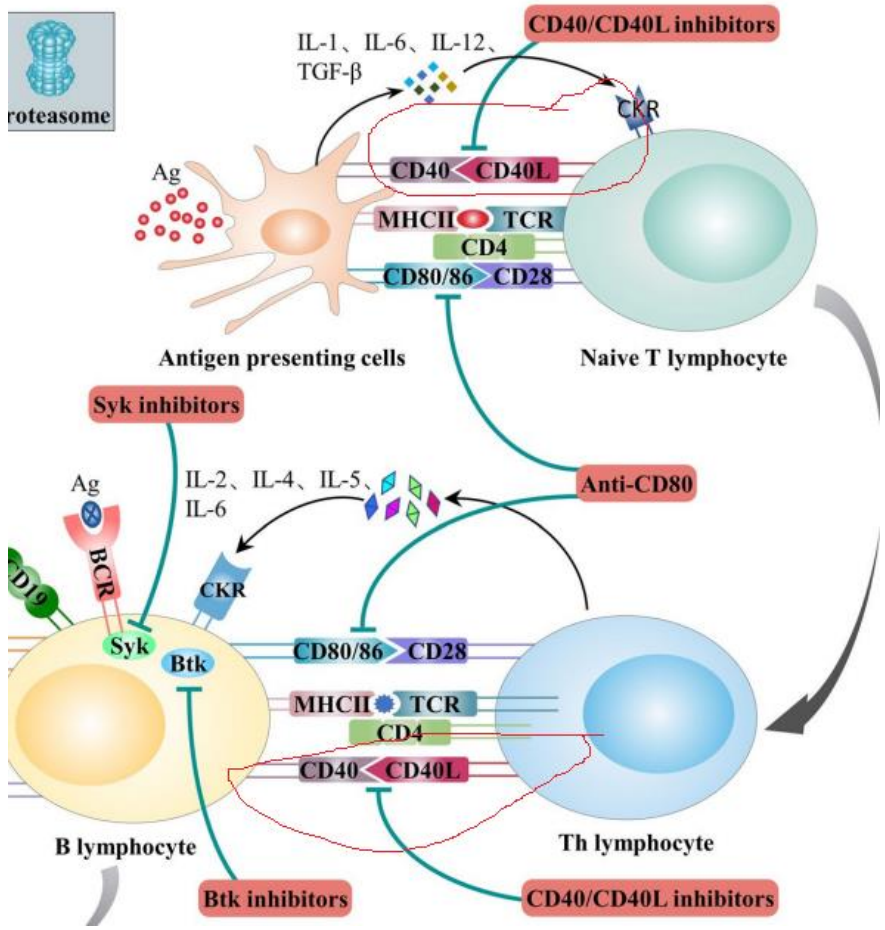
Immunotherapies Targeting T/B Cells: CD40/CD40L Inhibitors

- CD40 is a transmembrane receptor belonging to TNF receptor superfamily.
- Interaction between CD40 and CD40L plays an important role in regulating humoral and cellular immunity.
- It is essential for B-cell proliferation and differentiation, production of high-affinity antibodies, Ab class switching, costimulatory activity, and the activation of macrophages, dendritic cells and neutrophils.
- It can also regulate Th1 differentiation, CD8+ cytotoxic T lymphocyte (CTL) activation, and memory CTL maintenance.



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Immunotherapies targeting T/B Cells: CD40/CD40L Inhibitors

- Ruplizumab (BG9588), a 1st generation CD40/CD40L inhibitor, was the subject of a multicenter open-label phase 1/2 trial for the treatment of LN, but the trial was prematurely stopped due to thromboembolic events.
- 2nd generation CD40/CD40L inhibitors, such as dapirolizumab pegol (CDP7657), BI 655064, and iscalimab (CFZ533), were developed to prevent thromboembolic events.
- Dapirolizumab pegol did not reach primary goals in SLE treatment.
- RCTs on iscalimab are ongoing.

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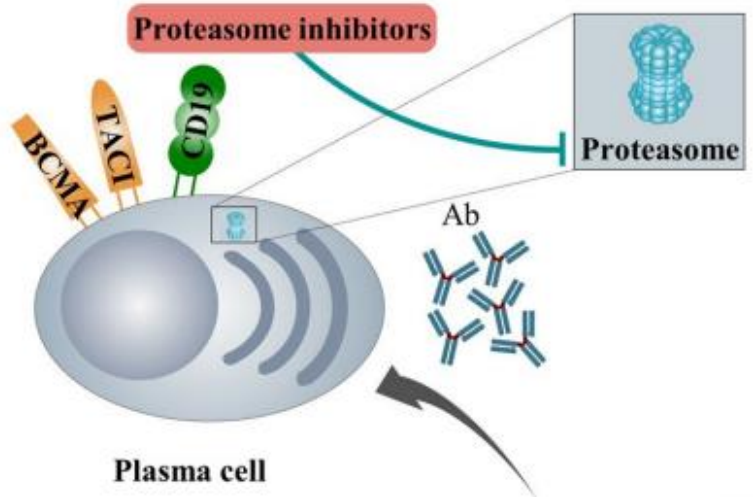
Immunotherapies Targeting T/B Cells: Proteasome Inhibitors

- The proteasome–ubiquitin system, a tightly regulated protein degradation system.
- Plays critical roles in many important biological processes, including MHC-mediated antigen presentation, cytokine and cell cycle regulation, and apoptosis.
- Proteasome inhibitors can cause many misfolded proteins to accumulate in the plasma cell endoplasmic reticulum and eventually leading to plasma cell cycle arrest and apoptosis.
- Plasma cell apoptosis causes a reduction in pathogenic autoimmune antibody levels.
- In addition, proteasome inhibitors can selectively target pro-inflammatory cytokines and their receptors, as well as interfere with intracellular signaling pathways within pro-inflammatory immune effector cells, which ultimately inhibits autoimmune responses.



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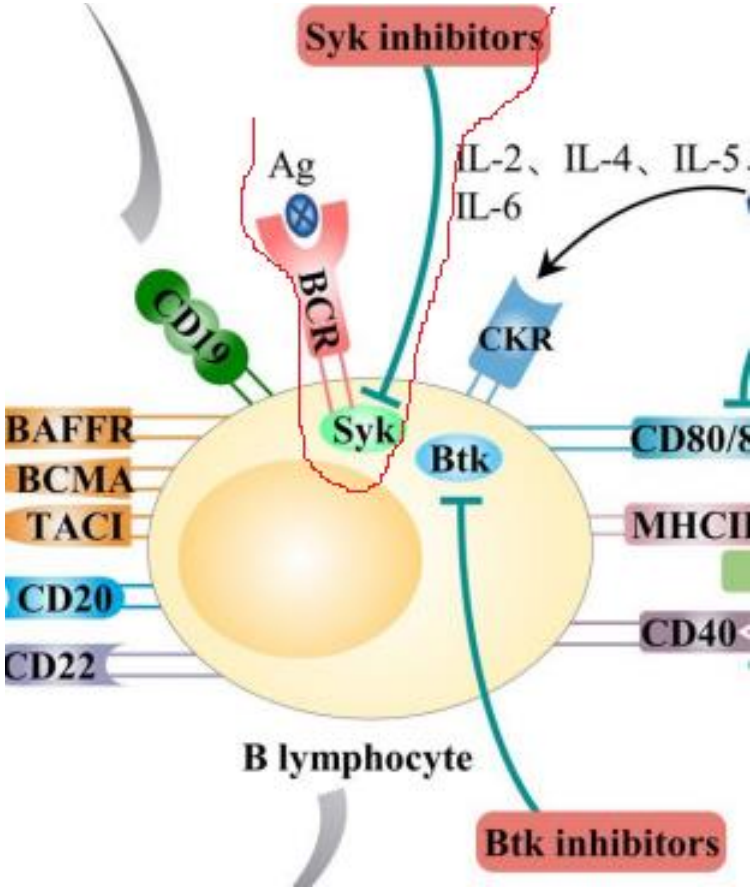
Immunotherapies Targeting T/B Cells: Proteasome Inhibitors

- Bortezomib, Carfilzomib
- Bortezomib approved for some types of lymphoma, multiple myeloma, AMR in SOT. Vial 3.5 mg and 1 mg. IV, SC.
- Carfilzomib: Approved for SOT desensitization, multiple myeloma. Vial 10, 30, 60mg. IV.
- RCTs and other small studies on Bortezomib in LN: Contradictory results on proteinuria, kidney function, level of autoantibodies. Needs more evidence.
- ADRs: fever, headache, facial swelling, liver dysfunction, and thrombocytopenia.
- Small uncontrolled studies or case reports/series in IgAN, MN, AAV. Needs more studies.

1.Tang B, et al. Clinical and Experimental Medicine. 2023; 23: 4091.
2.Lexicomp 2024

Immunotherapies Targeting T/B Cells: Spleen Tyrosine Kinase (Syk) Inhibitors

- Syk is a cytoplasmic nonreceptor protein tyrosine kinase expressed in various cell types, such as B cells, immature T cells, mast cells, neutrophils, macrophages, and platelets.
- Syk-mediated BCR signaling is indispensable for B-cell maturation and survival.
- Fostamatinib, a small molecule Syk inhibitor, has been approved by FDA for chronic refractory ITP. Oral tab 100mg, 150mg
- Is currently under investigation for the treatment of IgAN.



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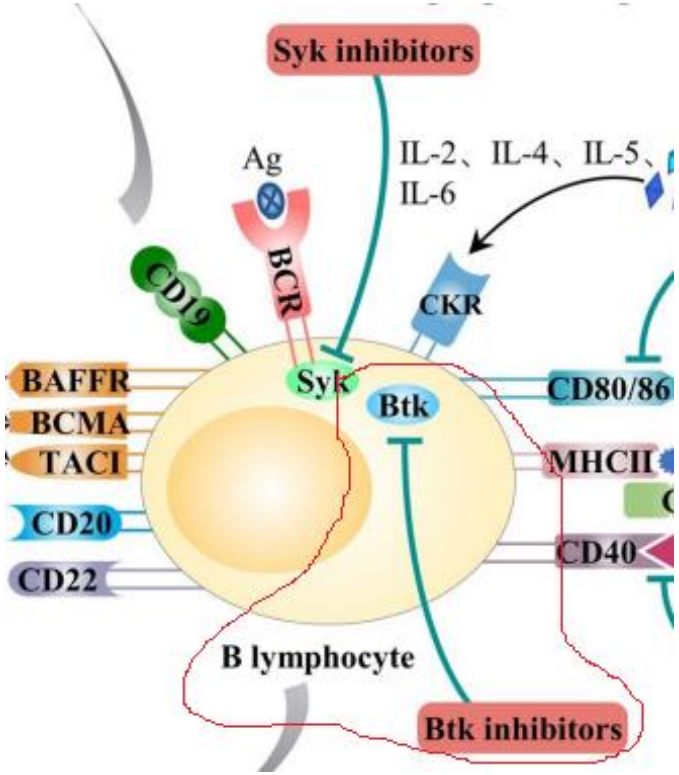
Immunotherapies Targeting T/B Cells: Bruton Tyrosine Kinase (Btk) Inhibitors

- Btk is a cytoplasmic nonreceptor protein tyrosine kinase that is expressed in a variety of immune cells, including monocytes, macrophages, basophils, mast cells, and B cells.
- Btk regulates signals downstream of the BCR, the Fc receptor, and Toll-like receptors.
- Btk inhibitors affect the survival of B cells, reducing production of autoantibodies.
- Regulate signal transduction mediated by Toll-like and Fc receptors to mitigate the damage caused by autoantibody deposition in tissue.
- Evobrutinib, fenebrutinib. Studied in LN but failed up to now.



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Immunotherapies Targeting Complement System

MBL: Mannan-Binding Lectin

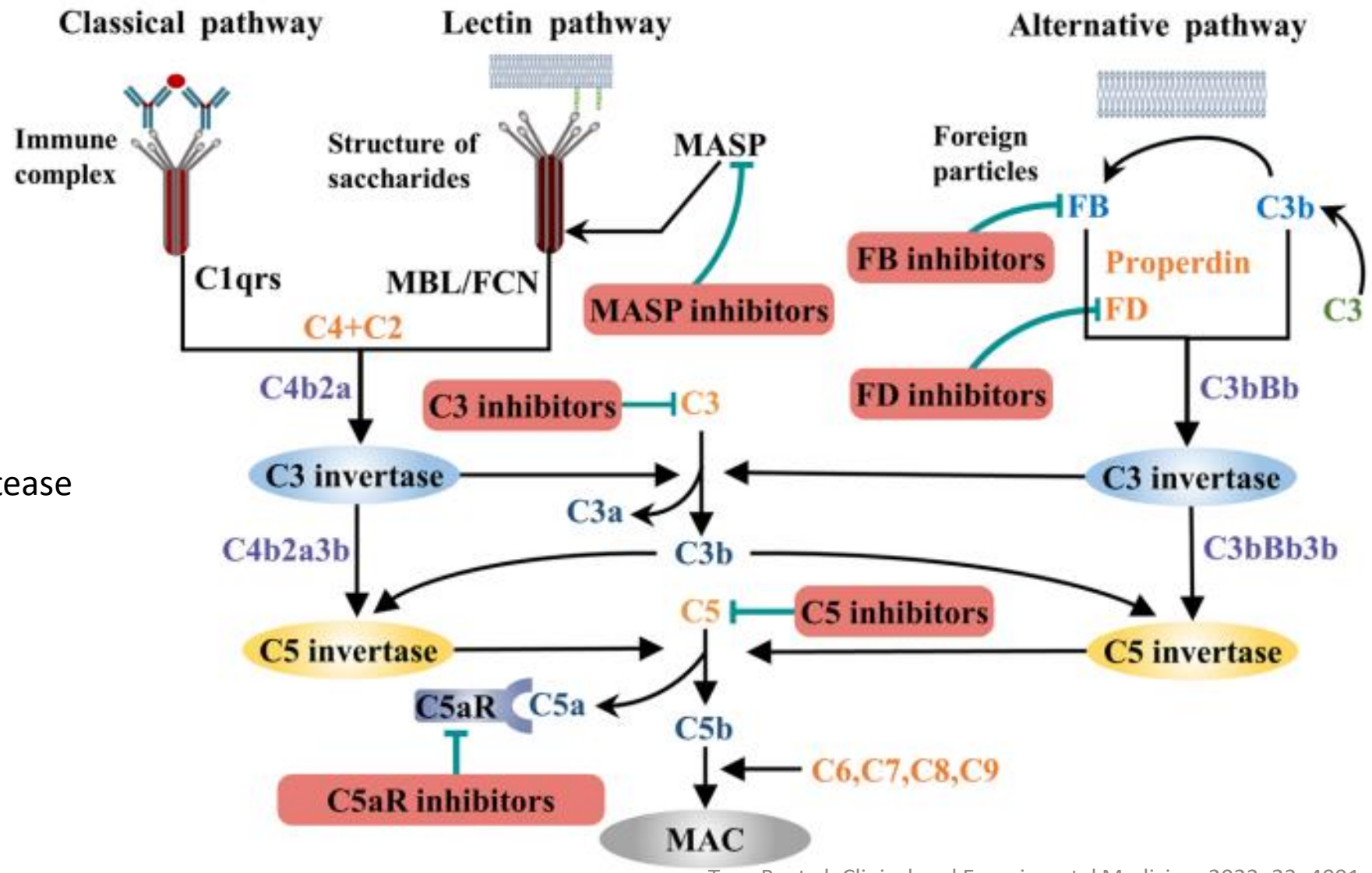
FCN: Ficolin

MASP: MBL Associated Serine Protease

FB: Factor B
FD: Factor D

C5aR: C5a Receptor

MAC: Membrane Attack Complex



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Immunotherapies Targeting Complement System

The complement system is not only the central component of innate immunity but also the bridge between innate immunity and the adaptive immune response.

Complement activation has been confirmed to be involved in the occurrence and progression of many renal diseases, such as aHUS, C3GN, AAVs, IgAN, LN, and MN.

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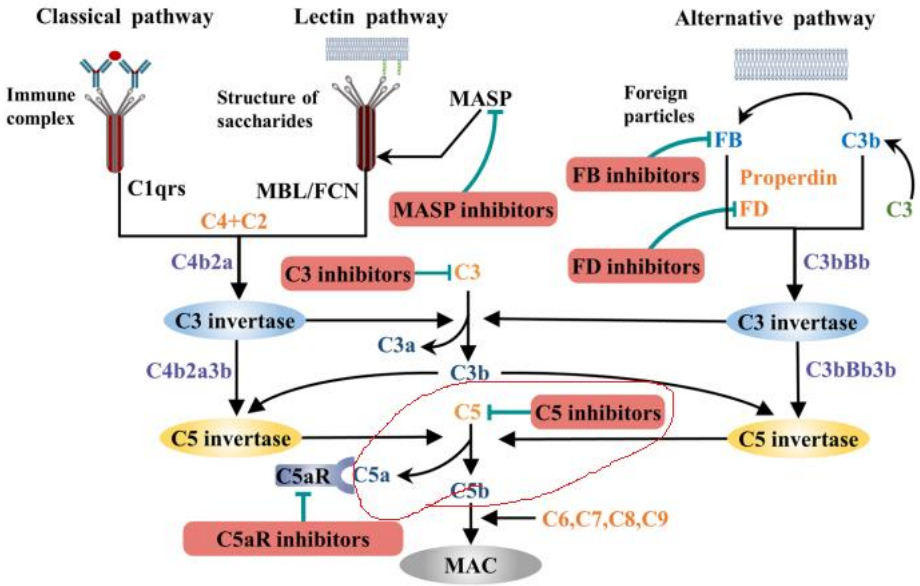
Immunotherapies Targeting Complement System C5 Inhibitors

- C5 inhibitors (eculizumab, ravulizumab and crovalimab) block the formation of the MAC by inhibiting the cleavage of C5 into C5a and C5b.
- Eculizumab, a humanized anti-C5 mAb, is the first complement inhibitory drug approved by the FDA.
- Ravulizumab, another anti-C5 mAb, was developed on the basis of eculizumab and shares the same mechanism, but has a longer half-life.
- Eculizumab and ravulizumab have been approved by FDA and EMA for aHUS.
- Both are IV injectable.
- Both as vial 300 mg/3ml. Iranian generic of eculizumab is available.



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Immunotherapies Targeting Complement System C5 Inhibitors

- A few retrospective/prospective studies showed that eculizumab is also effective in some patients with C3GN.
- Nevertheless, the effect of eculizumab in patients with C3GN is limited because eculizumab is not able to directly block C3 cleavage product-mediated glomerular injury.
- In addition, due to the rarity of C3GN, conducting large-scale RCTs to validate the therapeutic effect of eculizumab presents significant challenges.
- Therefore, eculizumab is currently used as the second-line treatment for C3GN.
- After some case reports, both are undergoing RCT in IgAN and LN.

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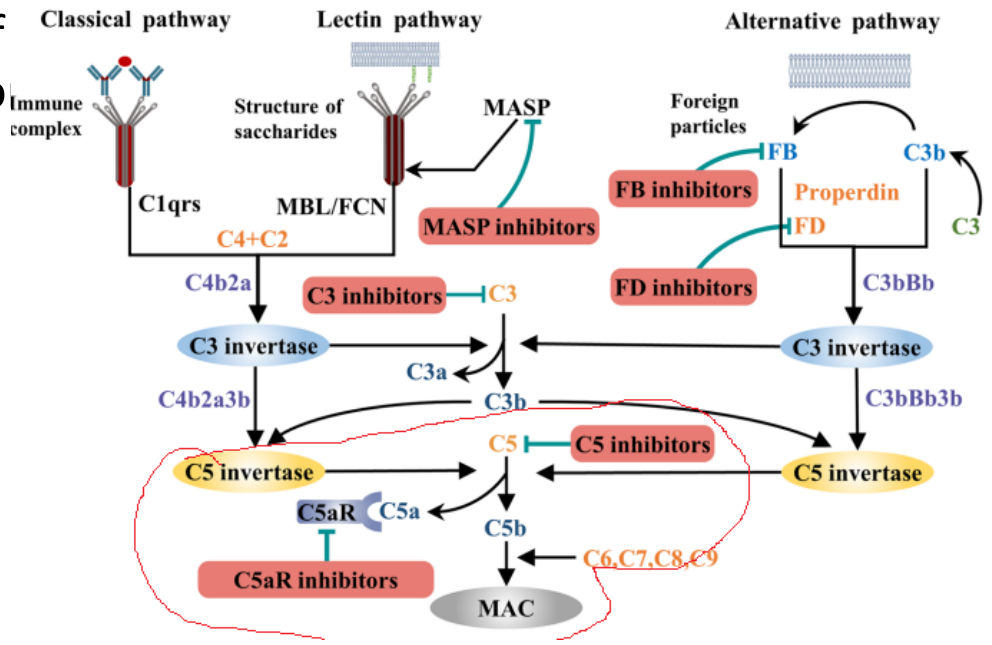
Immunotherapies Targeting Complement System C5a Receptor (C5aR)/C5a Inhibitors

- Avacopan is an oral C5a receptor-specific inhibitor that can block the binding of C5a and C5aR without affecting the production of C5b or the MAC, reducing the risk of side effects such as infectio
- Recent studies have revealed the importance of the interaction between C5a and C5aR in the development of AAVs.
- Avacopan approved by the FDA and EMA for AAVs.
- 30 mg BD with food for better absorption
- ADRs: Liver injury, HBV reactivation, angioedema, ↑risk of infection
- Substrate of CYP3A4.
- Some reports on its effect in IgAN. Needs more studies.
- Vilobelimab, a mAb directly targeting C5a which also blocks the interaction of C5a with C5aR, is undergoing RCTs for management of AAVs.



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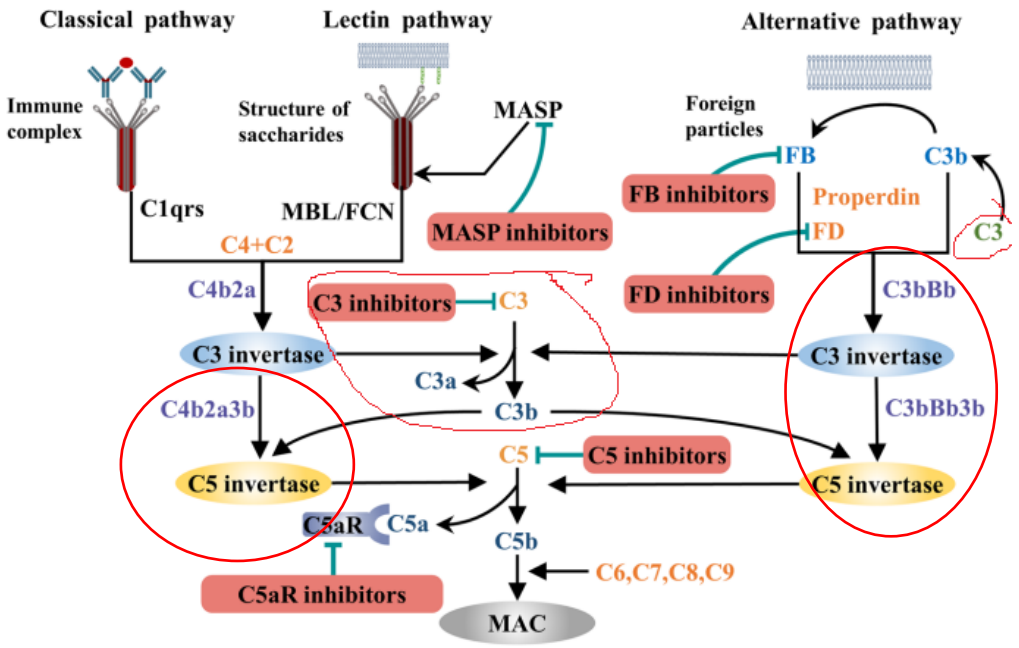
Immunotherapies Targeting Complement System C3 Inhibitors

- Pegcetacoplan is a C3 inhibitor that not only binds to C3 and C3b to inhibit their activation but also inhibits the activity of invertase containing C3b subunits, including C3 and C5 invertase associated with the alternative pathway and C5 invertase associated with the classical pathway.

- FDA approved for PNH.
- Solution 1080mg/20ml for SC infusion over 30-60min.

- Phase 2/3 clinical trials are evaluating its efficacy and safety in the treatment of C3GN.



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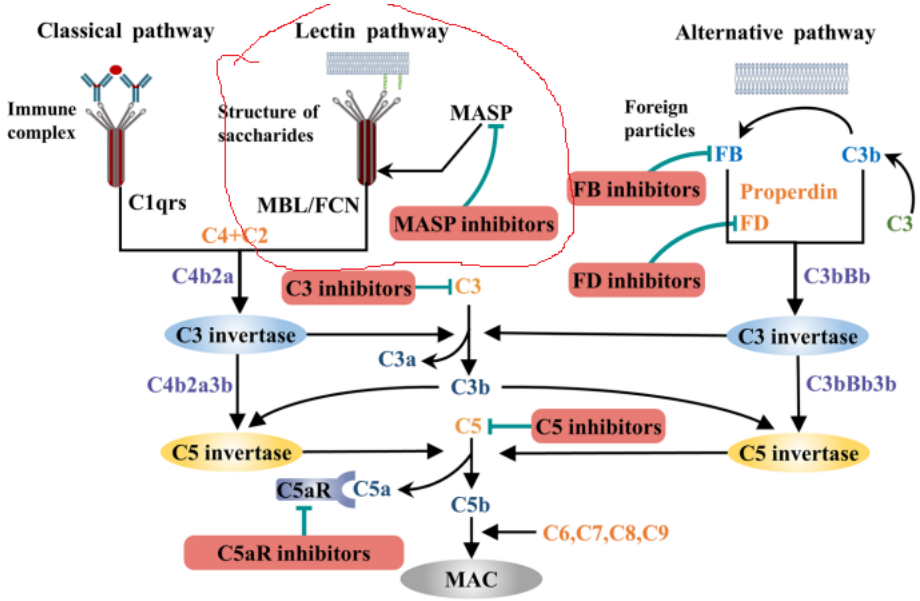
Immunotherapies Targeting Complement System
Anti-MASP2 Monoclonal Antibody

- Narsoplimab (OMS-721) is an anti-MASP2 mAB that blocks the initiation of the lectin pathway by inhibiting MASP2, thereby affecting the production of the MAC.

- Undergoing studies for IgAN, LN, MN, C3GN, and aHUS.



MBL: Mannan-Binding Lectin
FCN: Ficolin
MASP: MBL Associated Serine Protease

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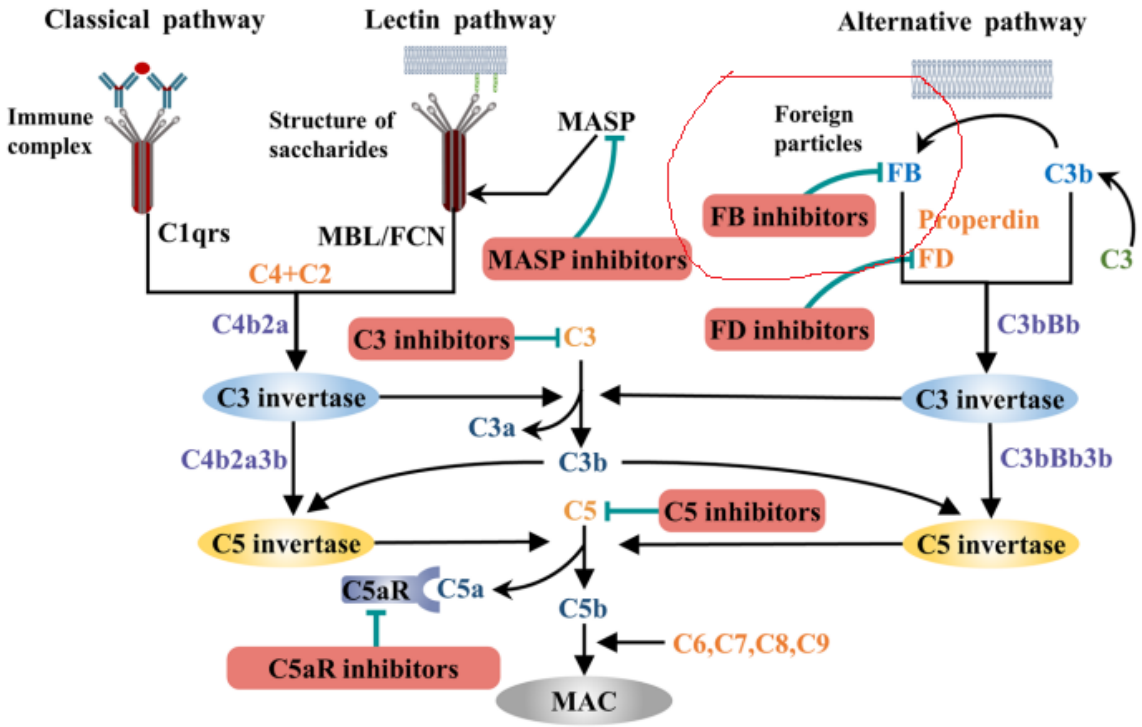
Immunotherapies Targeting Complement System Factor B Inhibitors

- Iptacopan (LNP-023) is an oral specific inhibitor of factor B that blocks the initiation of the alternative pathway.
- Under studies for C3GN, IgAN, aHUS, and LN.



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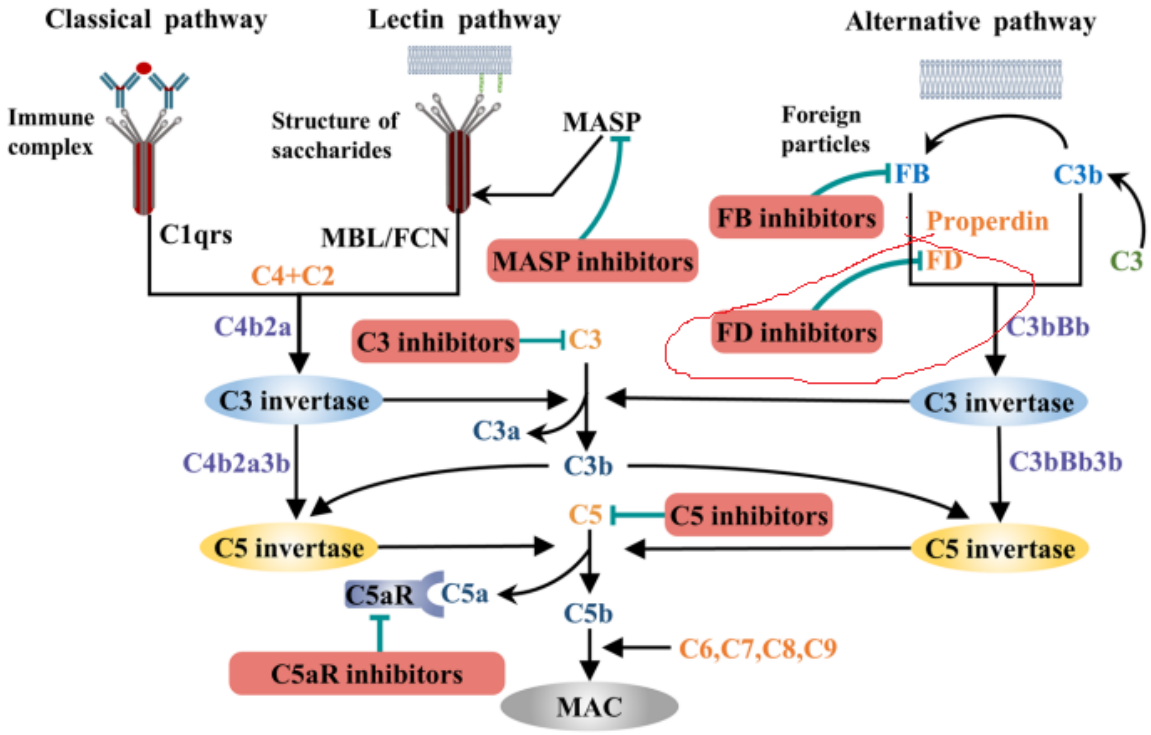
Immunotherapies Targeting Complement System Factor D Inhibitors

- Danicopan is a factor D-specific inhibitor that can inhibit the initiation of the alternative pathway.
- Expected to be studied for aHUS and C3GN.



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