Paroxysmal Noctural Hemoglobinuria (PNH) in the Era of New Therapies in the Pipeline

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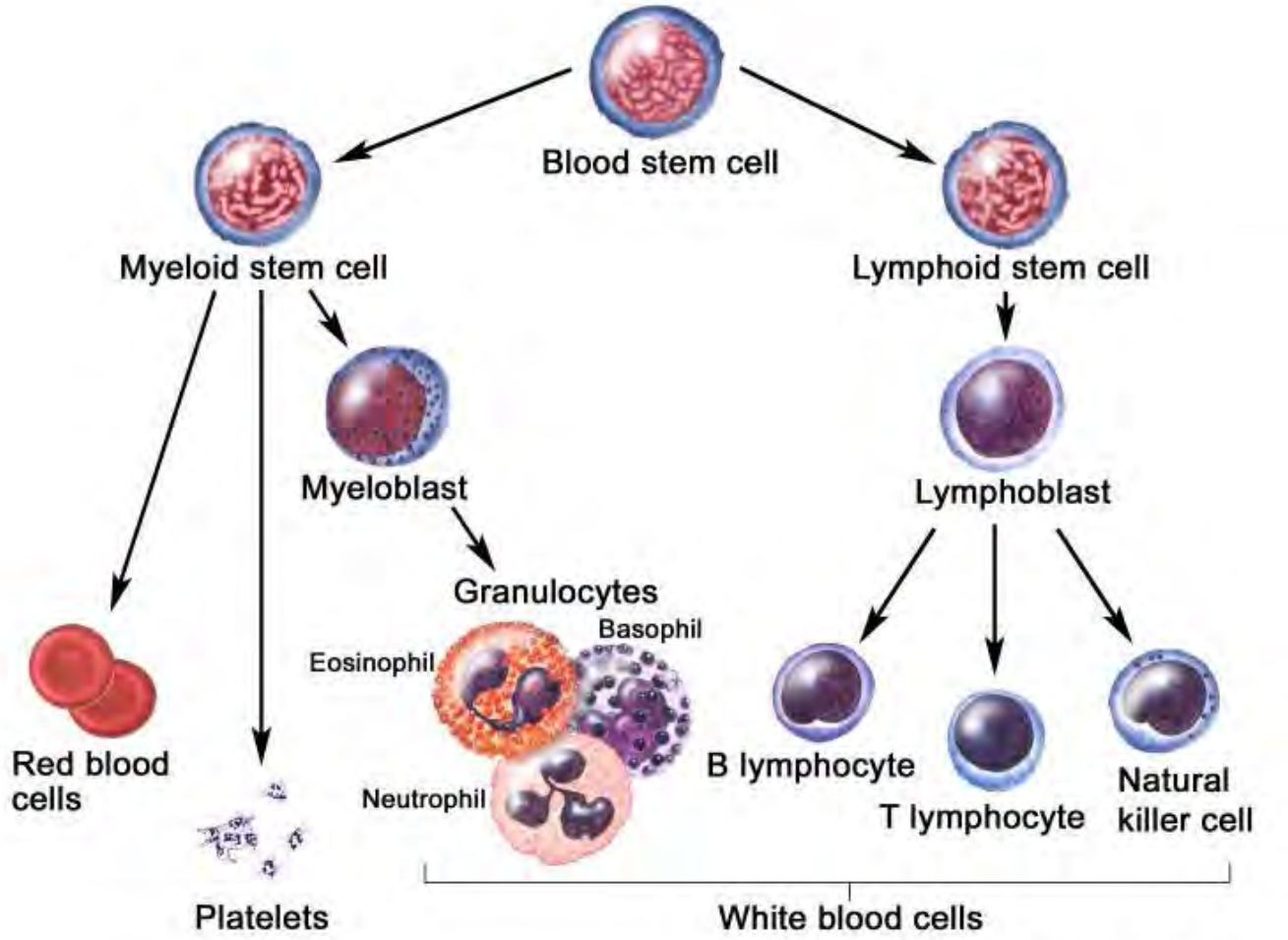
Paroxysmal Noctural Hemoglobinuria

Acquired somatic mutation in PIGA gene, which causes defective synthesis of the GPI anchor proteins (~20 proteins) leading to development of PNH and clinical manifestations.

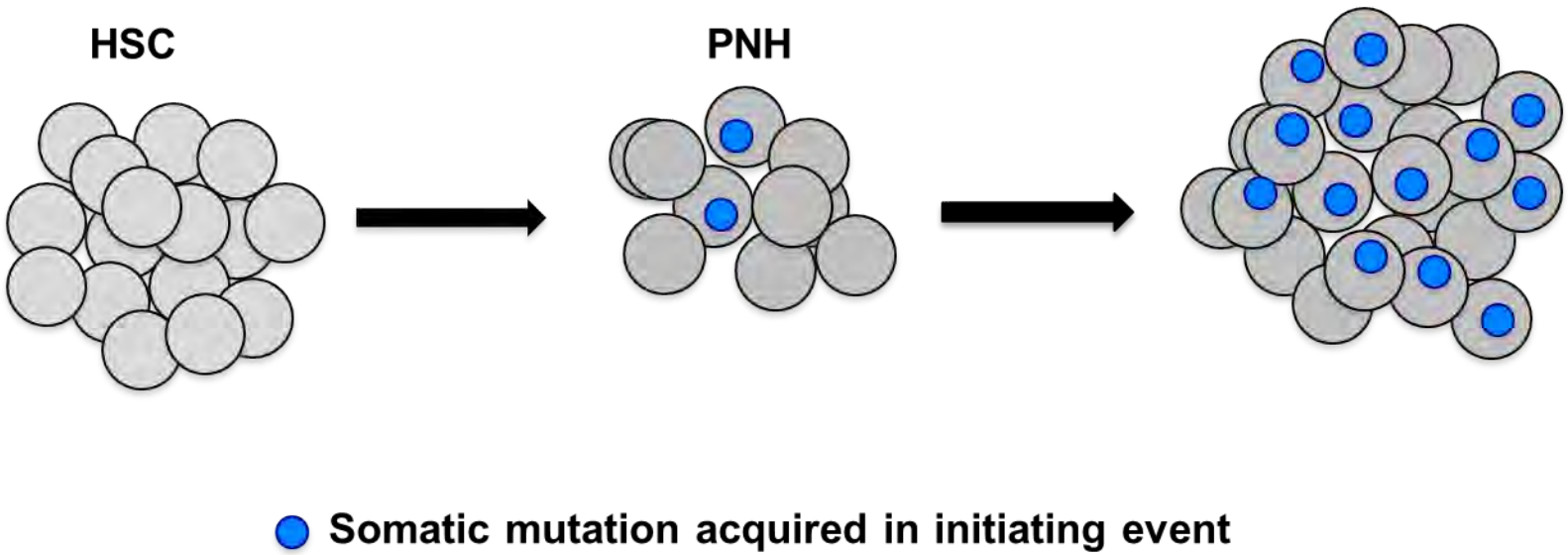
PIGA mutation can be found in small numbers of hematopoietic stem cells in normal individuals.

Characterized by hemolysis due to the action of complement on abnormal RBCs lacking CD55 and CD59. PNH RBC’s lyse more readily in the presence of activated complement. Note PNH granulocytes and platelets are sensitive to complement as well.

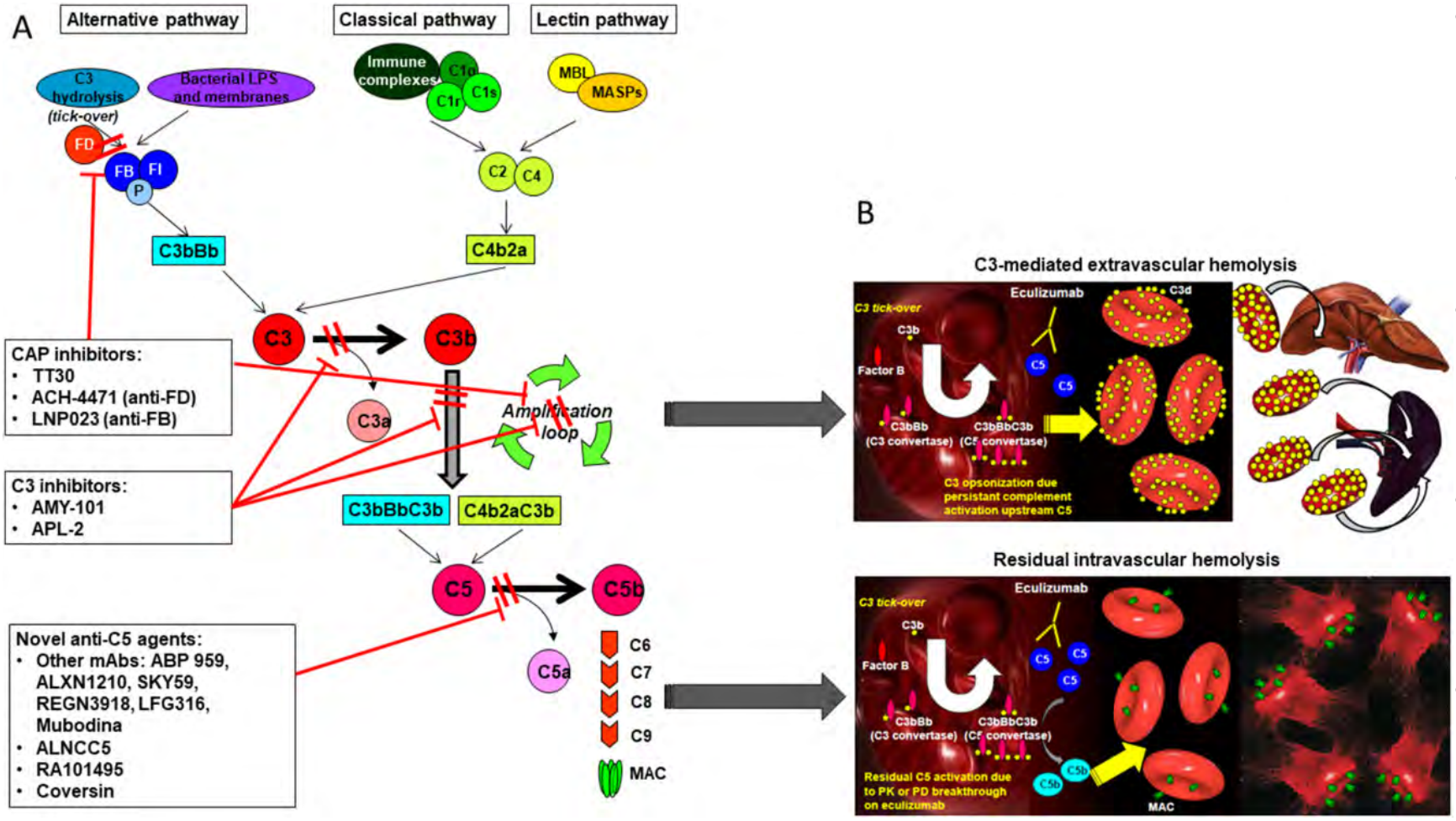
A BLOOD STEM CELL CAN GIVE RISE TO ALL THE CELLS OF THE BLOOD



Pathophysiology



Complement System



- Complement is a group of proteins that are part of our immune system.
- Complement circulates in an inactive form.
- Many different events can activate complement including trauma, infection, stress, etc.
- Complement will attack certain bacteria by making pores in the surface of the bacteria.
- In PNH, activated complement will attack red cells causing them to “lyse” (burst)

Risitano AM, Marotta S. Toward complement inhibition 2.0: Next generation anticomplement agents for paroxysmal nocturnal hemoglobinuria. Am J Hematol. 2018 Aug;93(4):564-577. doi: 10.1002/ajh.25016. Epub 2018 Jan 25. PMID: 29314145.

Clinical Presentation

Hemolytic anemia (varying degree of anemia)

-Symptoms of back or abdominal pain, headache, fever, esophageal spasm , erectile dysfunction, renal insufficiency, thrombosis, and pulmonary hypertension

-Exacerbation of hemolysis can occur with infection, surgery, or transfusions

Note aplastic anemia can be diagnosed both before or after the identification of PNH.

-PNH clones are presents in 20% of AA pts and 20% of pts with MDS.

-An increased incidence of acute leukemia

Thrombotic (blood clots) complications

-Venous thrombosis (extremities)

-Budd-Chiari syndrome (thrombosis of hepatic veins)

-Intra-abdominal, cerebral (strokes), and venous sinus thrombosis

-Thrombotic tendency is enhanced during pregnancy

Labs

Labs:
Elevated LDH, D-dimer, low haptoglobulin, and either elevated/decreased reticulocytosis

No specific morphologic abnormalities of the RBCs in PNH on smear, but BM reveals erythroid hyperplasia.

Late occurring iron deficiency anemia because of chronic urinary loss from intravascular hemolysis.

Commonly see some degree of leukopenia or thrombocytopenia

Diagnosis

By flow cytometry, due to increase sensitivity to detect small abnormal populations, because monocytes and granulocytes have shorter half lives and numbers not affected by transfusions, analysis of GPI anchored proteins on neutrophils or monocytes is preferred.

FLARE assay binds selectively with high affinity to GPI anchor of most cells lineages, most useful to assay the GPI anchor on granulocytes.

Type 1- no deficiency
Type 2- partial deficiency of CD55/59
Type 3- complete deficiency of CD55/59

PNH Therapeutic Approaches

Curative approaches

- In general restoration of healthy stem cell compartment
- Eradication of PNH stem cells not sufficient

HSC transplant

- Role now limited to specific situations
- One has to be “into the cure” and willing to pay for the chance of cure i.e. there may be cost in terms of the risk of complications
- In case control study, inferior survival to eculizumab-treated patients
- Once/if successful --- significant improvement of quality of life

What are the indications

- Intractable recurrent thrombosis despite adequate anticoagulation
- Refractory pancytopenia

PNH Therapeutic Approaches

Supportive approaches

- **Transfusions for anemia**
- **Treat iron overload if progressive**
- **Anti-coagulation for prevention of thrombosis after an acute thrombotic episode**

Increase red cell production:

- **Aranesp/Procrit if Epo levels low and reticulocyte count low**
- **Optimize iron level if low**
- **Cyclosporin/Tacrolimus if low reticulocyte/platelet count**
- **Anabolic steroids +/-prednisone**

Complement inhibition/less activation

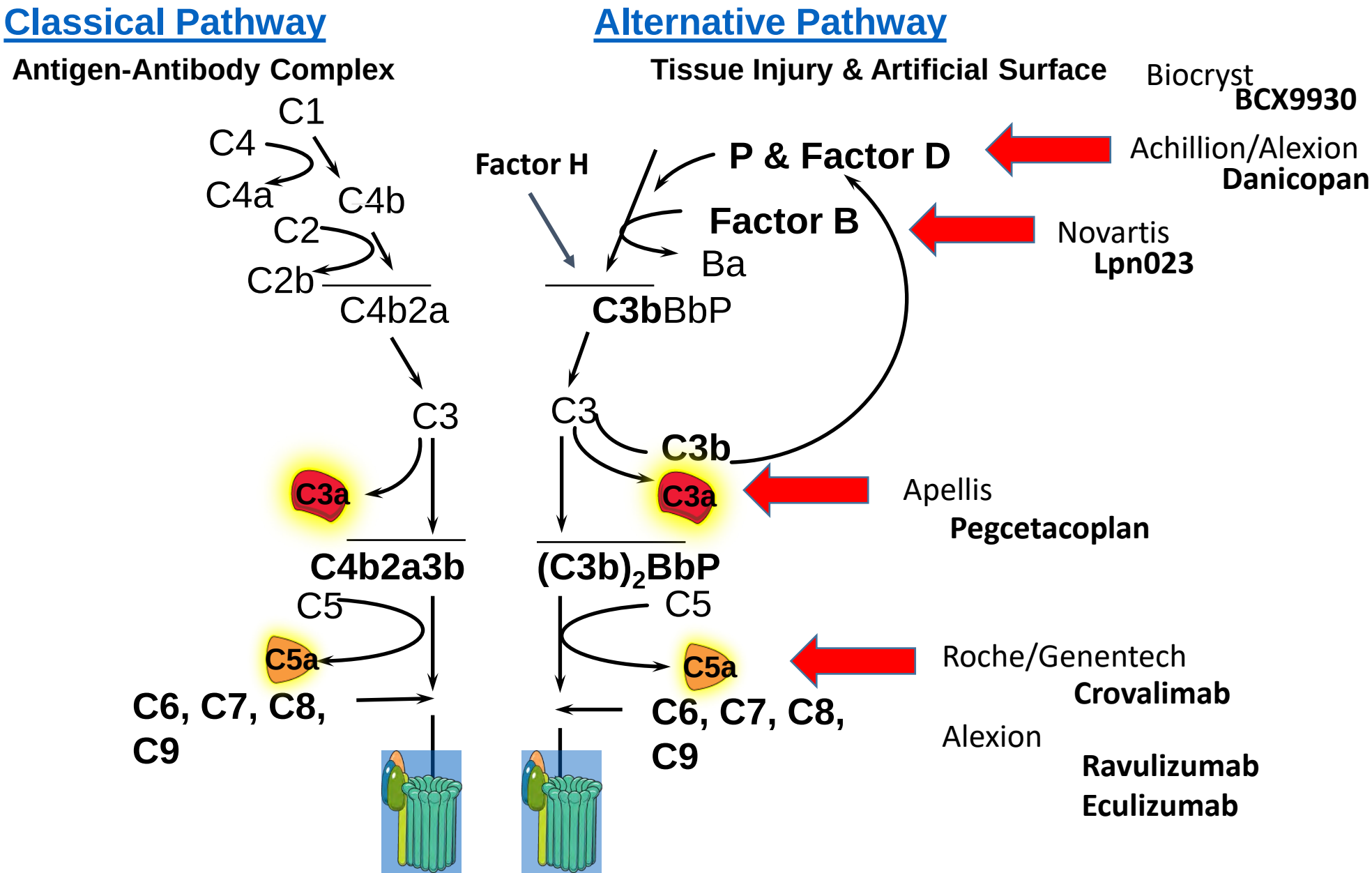
- **Acute crisis: Medrol pack/transfusion/hydration**
- **Chronic : Anabolic steroids +/-prednisone**

} Old days

Acute and chronic hemolysis:

- **Complement inhibitors** Current treatment

Complement Inhibition



Current Treatment

Humanized monoclonal antibody eculizumab or ravulizumab

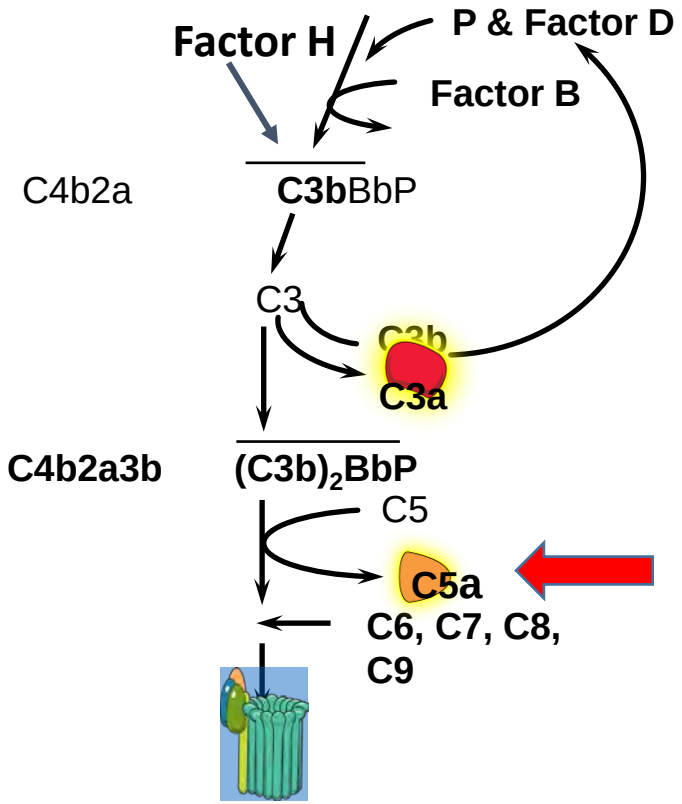
Binds the complement component C5, thereby inhibiting terminal complement activation, decreased hemolysis of RBCs, and tendency of thrombosis, but does not fix the defect in hematopoiesis

Reduces intravascular hemolysis not extravascular hemolysis

Vaccinate 2 weeks prior to treatment with menactra due to risk of meningitis (Neisseria) secondary to complement inhibition. Then revaccinate every 3-5 years.

C5 Inhibitors

Current: **Ultomiris** q8 weeks
Soliris q2 weeks



Benefits: improved well being: improved anemia, less hemolysis less thrombosis

Downside: bound to the treatment, not always full response, some refractory patients, major inconvenience, risk of meningitis

Decision process: some clear indications other risk vs benefits, personal goals and fears

Likely same safety consideration As with soliris

Future coming soon: **crovalimab**

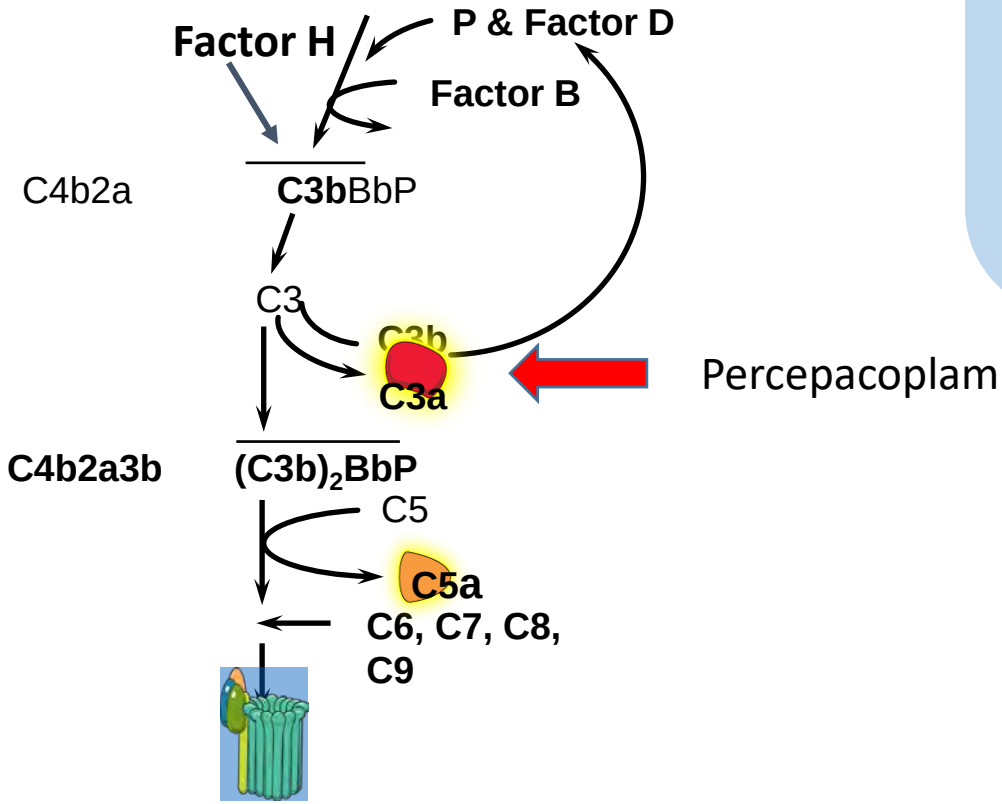
Self-injections every 4 weeks

pozelimab

Self-injections every 4 week following an initial loading dose

Similar or better efficacy and but unlikely rescues eculizumab non responders

C3 Inhibitor



Percepacoplam

Benefits: Appears to be superior in non responders to eculizumab and can replace infusion of anti-C5 as a initial therapy, makes patient independent of infusion because self injected

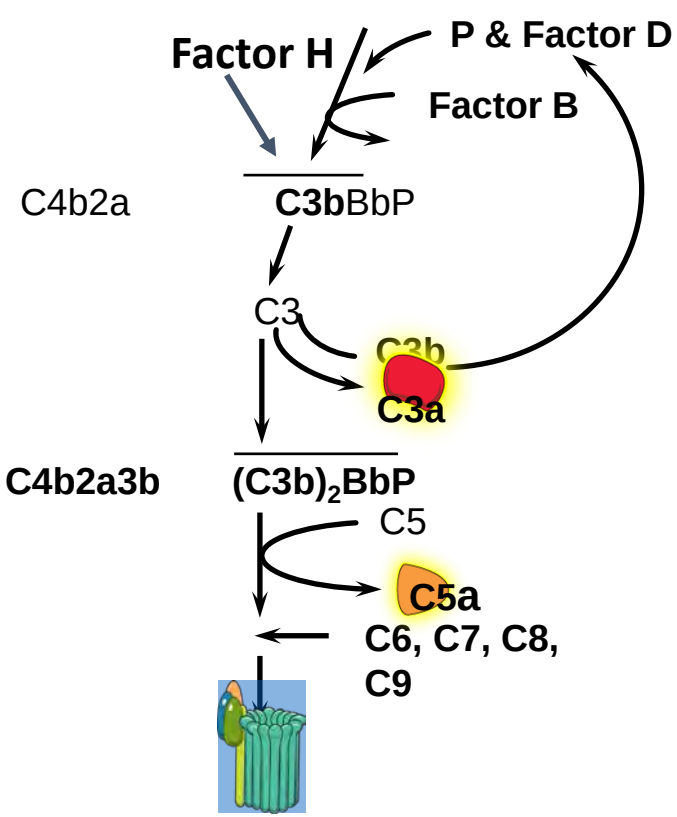
Improves extravascular hemolysis

Downside Every other day injection with 2 sticks, burdensome gadget and 30 min self-administration sc

No safety record as extensive as with C5 inhibitors

Other antibodies for C3 in development

Factor D Inhibitors



Biocryst
BCX9930

Achillion/Alexion
Danicopan

Improves extravascular hemolysis

Benefits: Oral drugs bid or tid a day
So far very effective in combination with C5 inhibitors
Likely effective also alone

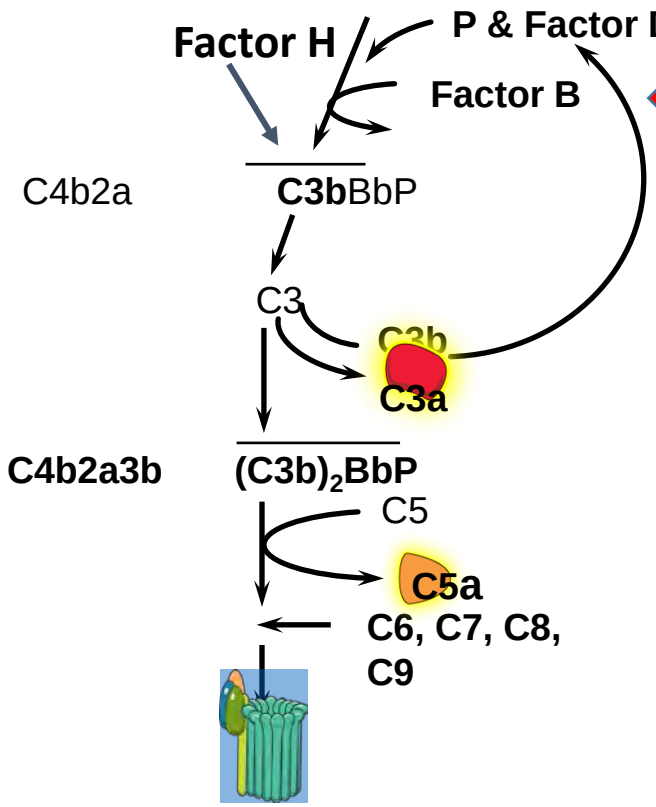
Danicopan will be tested and likely used with ultomiris or soliris

BCX9930 will likely be developed as a single agent

Both drugs can rescue refractory

No safety record as extensive as with C5 inhibitors

Factor B Inhibitor



Novartis
Lpn023

Benefits: Oral drug 2 x a day
So far very effective in combination with C5 inhibitors and alone

Appears so effective that the trials aim of complete remission rate

Will likely be developed as a single agent or to rescue non responders to other therapies

Improves extravascular hemolysis

No safety record as extensive as with C5 inhibitors

Conclusion

There will be choices for therapy !

Patients may have preferences but we would bet on oral agents

Diffusional agents will get better and less dependent upon clinical visits

While cure is not in sight --- new drugs will convert this disease into a more manageable condition

Curative treatments are being conceptualized: there is more hope!!!!!

QUESTIONS?