Komplementtijärjestelmän säätelyhäiriöt glomerulonefriiteissä, fokuksessa MPGN (C3G) ja IgAGN

13.3.2020

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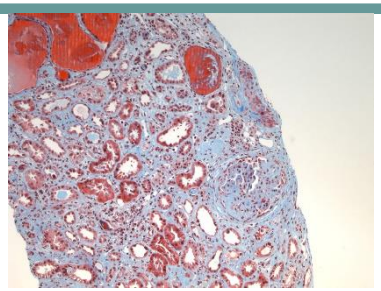
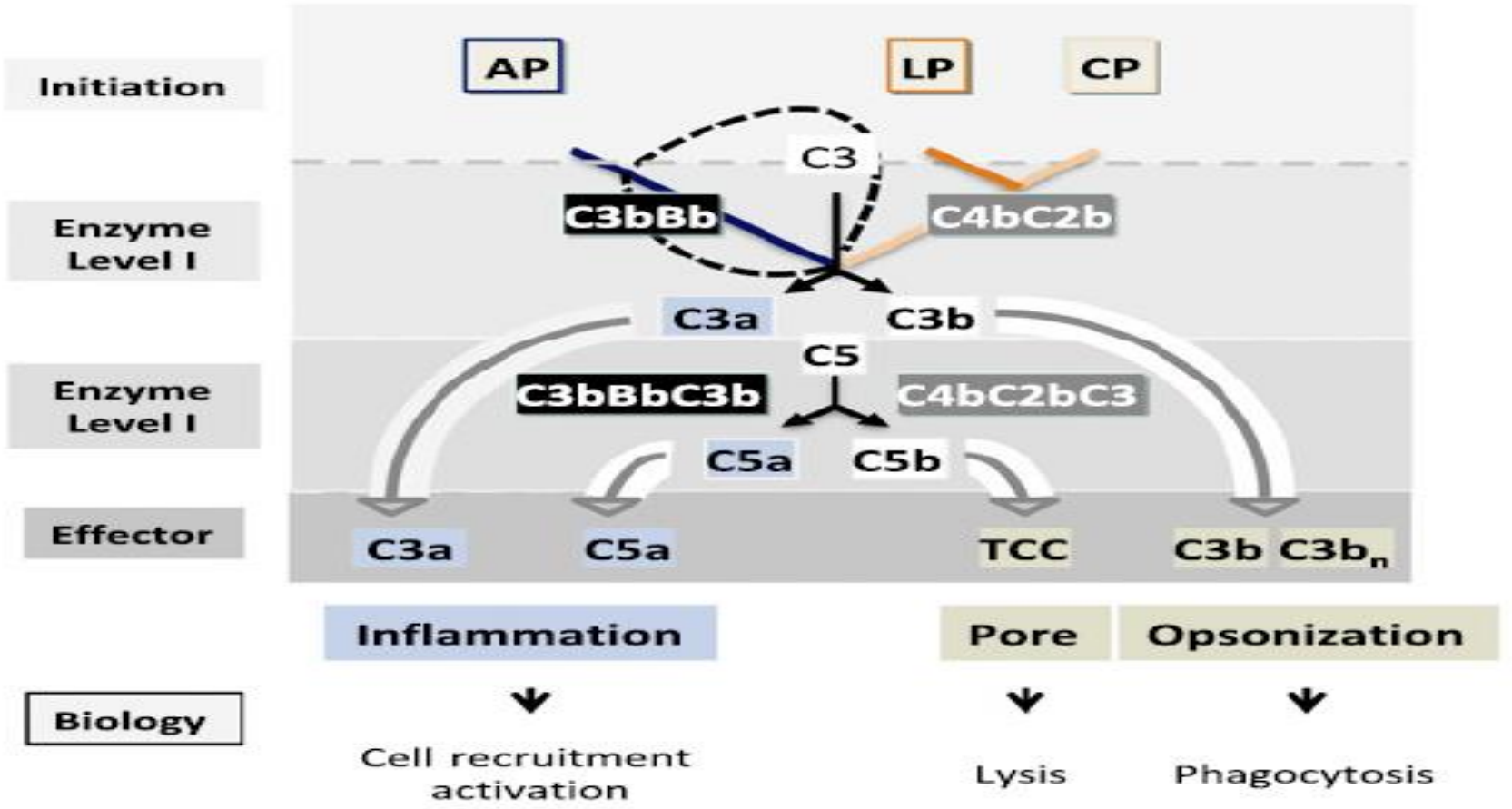
HYKS, vatsakeskus, nefrologian klinikka



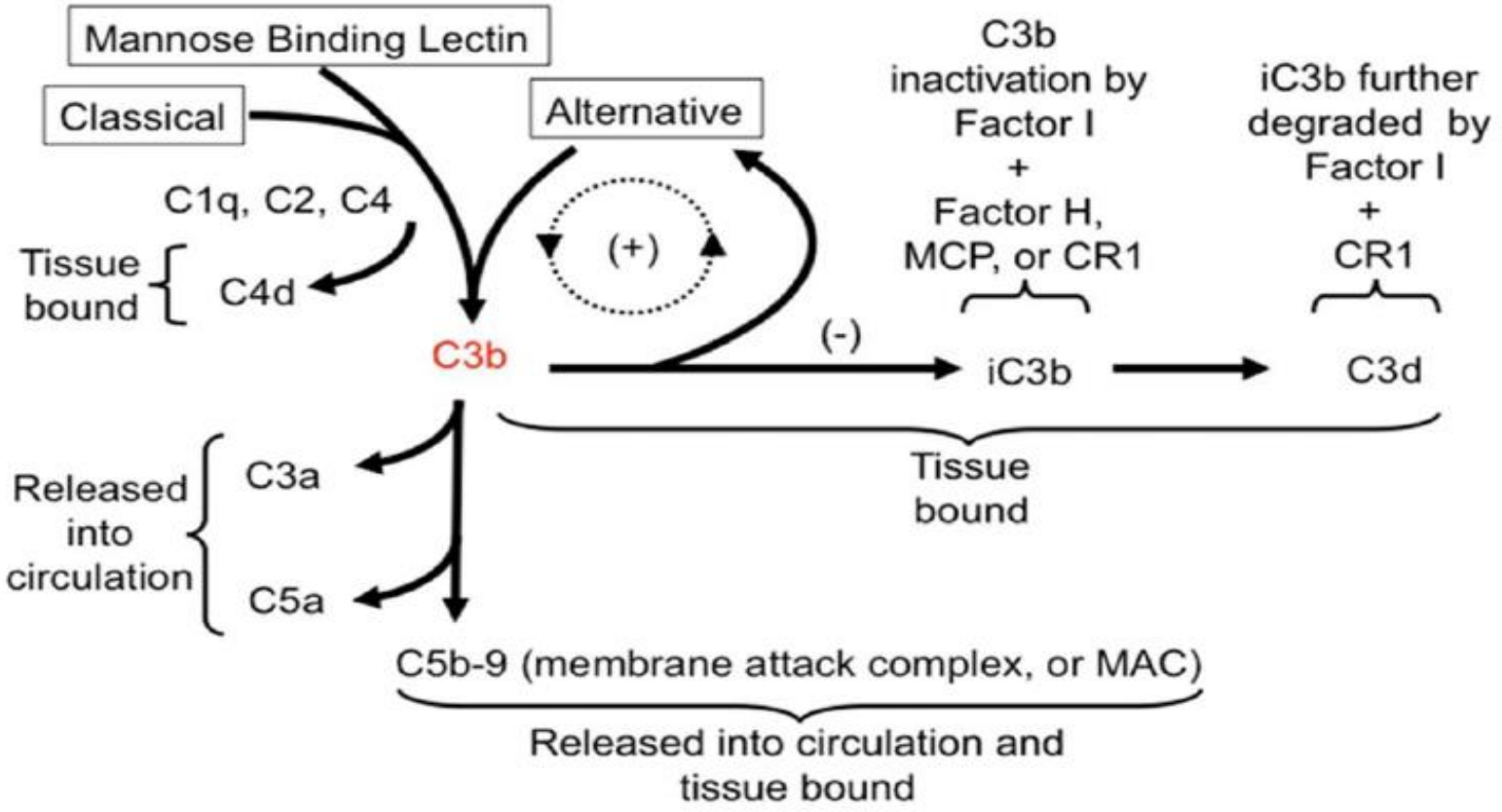
Sidonnaisuudet

- Luentoja tai muuta asiantuntijayhteistyötä: MSD, Novartis, Roche, Amgen, Sanofi, Novo Nordisk, AstraZeneca, Boehringer Ingelheim Finland
- Osallistunut useisiin koulutuksiin, joita sponsoroinut tai järjestänyt: Alexion, Roche, Amgen, Genzyme
- Tutkimusapuraha: Alexion, Novartis
- Pohjoismaisen komplementtikomitean jäsen: Alexion tukee toimintaa

Lyhyt kertaus komplementtijärjestelmästä, Zipfel et al. 2020



Kaikkien teiden aktivaatio johtaa siis C3-tasolle, Thurman 2015



Komplementtilääkkeitä kehitetään kiihtyvällä tahdilla, Zipfel et al. 2019

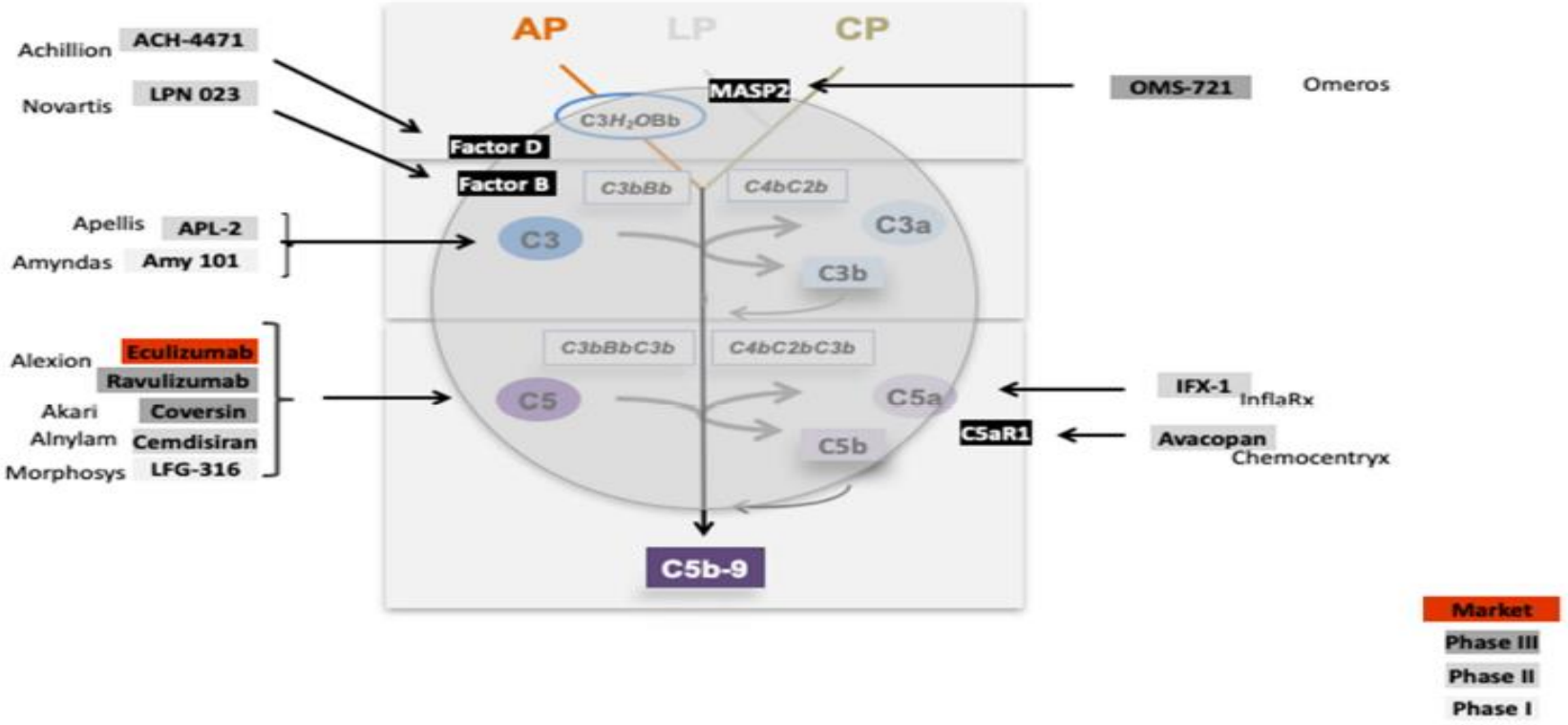
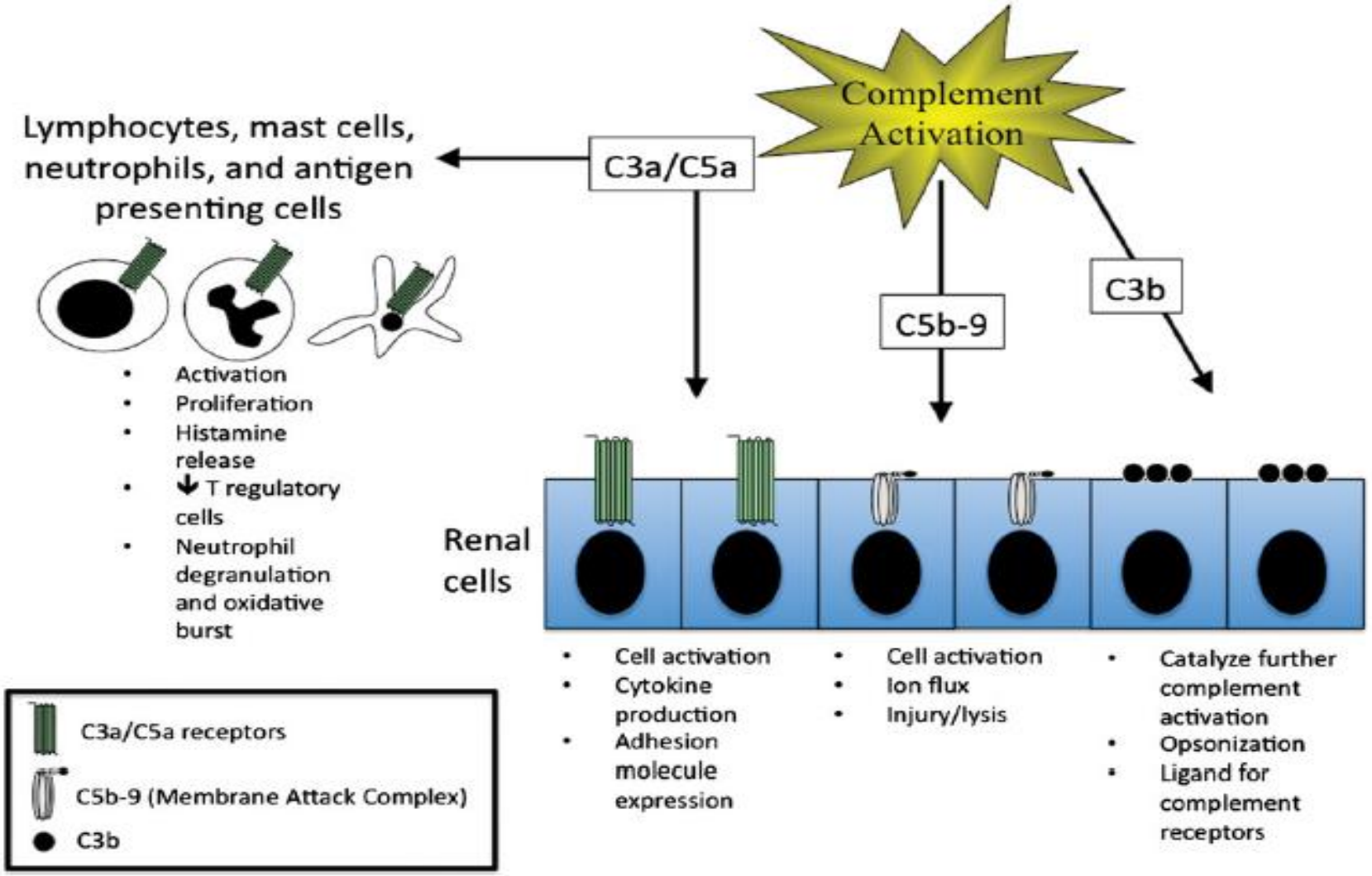


FIGURE 11 | Complement inhibitors target different levels and steps of the complement cascade. Complement inhibitors which are evaluated in clinical trials for various kidney diseases bind to different complement proteins and inhibit the cascade at different levels. C1 inhibitor binds to C1 and blocks C1 activation. OMS 721 binds to the lectin pathway protease MASP2. C3 targeting proteins include APL2 (Apellis) and AMY 101 (Amyndas). The Factor D inhibitor ACH-4471 (Achillion) binds to Factor D, a protease which cleaves in its active state Factor B. LPN023 (Novartis) a small Factor B binding protein blocks formation of the enzymatically active AP C3 Convertase. Several compounds target complement at the level of C5. Eculizumab, and the new version Ravulizumab (both Alexion) bind to C5 and block activation of the protein. Coversin is a tick derived C5 binding protein (Akari) and C5 inhibitor. C5 synthesis is blocked by Cemdisiran as an RNAi targeted strategy (Alnylam), and by LFG-316 (Novartis). The complement inflammatory C5a—C5aR1 axis is inhibited by IFX-1 (InflaRx) and Avacopan (Chemocentryx).

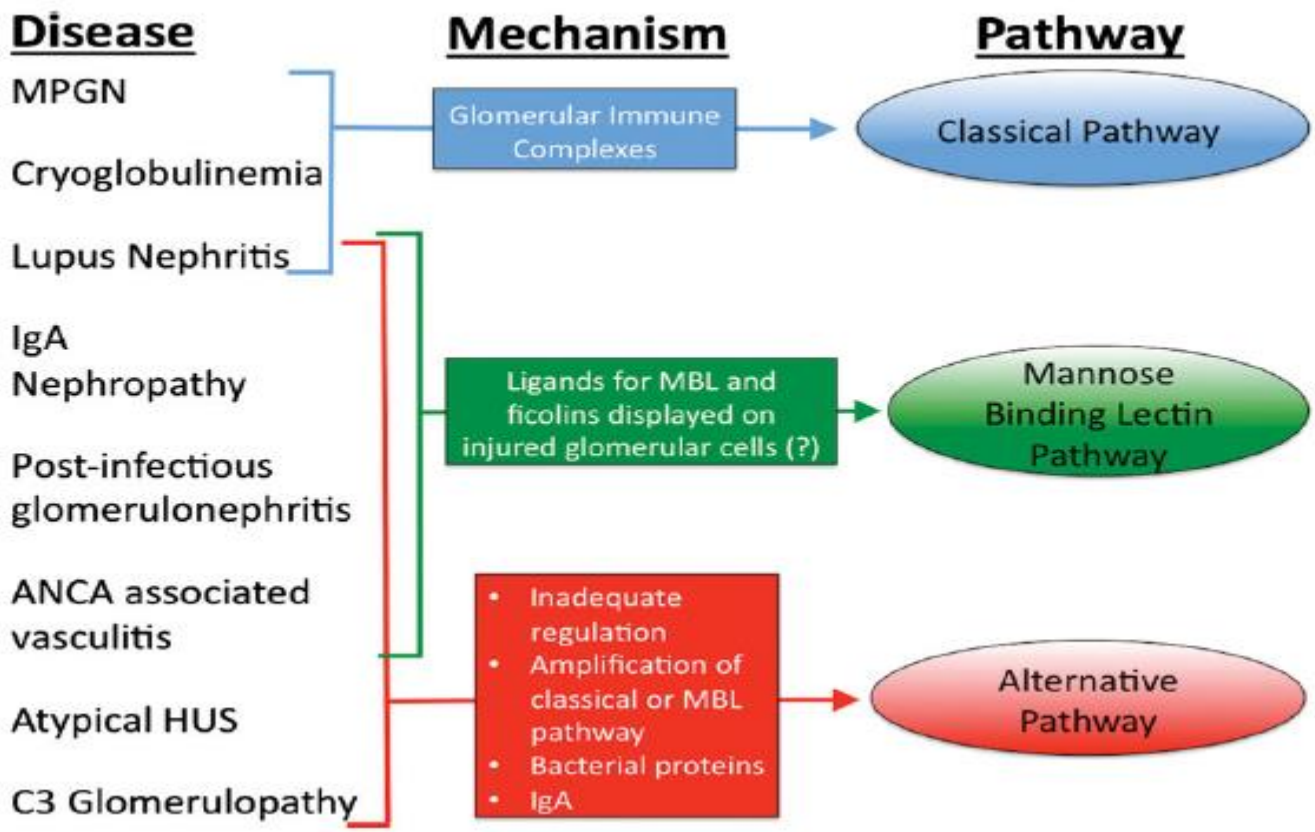
Komplementtilääkkeitä kehitetään useisiin nefrologisiin tauteihin, Zipfel et al. 2019

aHUS	OMS721	OMS 00620646	Antibody	MASP2	Omeros	III	NCT03205995	
	Eculizumab	Soliris	Antibody	C5	Alexion	**Market**		NCT02574403; Phase 4, duration of Eculizumab treatment
	Ravulizumab	ALXN1210	pH-dependent Antibody		Alexion	III	NCT03131219 NCT02949128	Ravulizumab is already approved for paroxysmal nocturnal haemoglobinuria
	Coversin (rVA576)	Nomacopan	Peptide		Akari Therapeutics	III	NCT03829449	
	CCX168	Avacopan	Small molecule	C5aR1	ChemoCentryx	II	NCT02464891	
ANCA-associated vasculitis	IFX 1	CaCP 29	Antibody	C5a	InflaRx	II	NCT03712345	Granulomatosis with Polyangiitis; Microscopic Polyangiitis
	CCX168	Avacopan	Small molecule	C5aR1	ChemoCentryx	III	NCT02994927	
C3 Glomerulopathy	OMS721	OMS 00620646	Antibody	MASP2	Omeros	II	NCT02682407	DDD
	AMY-101		Antibody	C3	Amyndas	I	NCT03316521	
	APL-2		Peptide		Apellis	II	NCT03453619	DDD and C3 glomerulonephritis
	ACH 4471	ACH-0144471	Small molecule	FD	Achillion	II	NCT03459443	DDD and C3 glomerulonephritis
							NCT03369236	DDD and C3 glomerulonephritis
							NCT03124368	DDD and C3 glomerulonephritis
	LNP023		Small molecule	FB	Novartis	II	NCT03832114	C3 Glomerulonephritis
	Eculizumab	Soliris	Antibody	C5	Alexion	I	NCT01221181	DDD and C3 glomerulonephritis
						II	NCT02093533	C3 glomerulonephritis
	CCX168	Avacopan	Small molecule	C5aR1	ChemoCentryx	II	NCT03301467	DDD and C3 glomerulonephritis
IgA nephropathy	OMS721	OMS 00620646	Antibody	MASP2	Omeros	III	NCT03608033	
	APL-2		Peptide	C3	Apellis	II	NCT03453619	
	LPN023		Small molecule	Factor B	Novartis	II	NCT03373461	
	Cemdisiran	ALN-CC5	RNAi	C5	Alnylam	II	NCT03841448	
	CCX168	Avacopan	Small molecule	C5aR1	ChemoCentryx	II	NCT02384317	
Immune complex membranoproliferative glomerulonephritis	ACH 4471	ACH-0144471	Small molecule	Factor D	Achillion	II	NCT03459443 NCT03124368	
Lupus nephritis	OMS721	OMS 00620646	Antibody	MASP2	Omeros	II	NCT02682407	
	APL-2		Peptide	C3	Apellis	II	NCT03453619	
Membranous nephropathy	OMS721	OMS 00620646	Antibody	MASP2	Omeros	II	NCT02682407	
	APL-2		Peptide	C3	Apellis	II	NCT03453619	

Komplementin aktivoituminen johtaa pro-inflammatoristen välittäjien syntyyn ja suoraan kudostuhoon munuaisissa, Thurman 2017

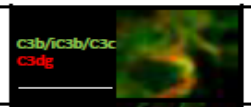
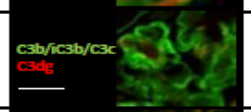
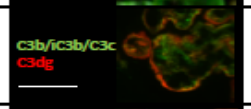
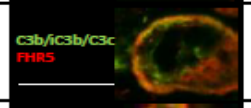
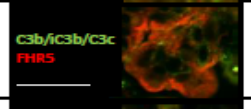
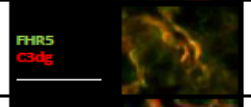


Komplementin aktivoituminen eri glomerulonefriiteissä, Thurman 2017



Munuaisbiopsian tulkinta saattaa jatkossa näyttää tältä, Medjeral-Thomas et al. 2019

Mitä histologian C3-löydös tarkoittaa:
Komplementin aktivaatio nyt vai menneisyydessä,
onko lokaalinen vai systeeminen aktivaatio ?

Immunofluorescence combination			Example	Consistent with antigen	Interpretation
C3b/iC3b/C3c	C3dg	FHR5			
+	+			C3b/iC3b/C3c and C3dg	Ongoing and previous local C3 activation AND/OR C3c from local and/or systemic complement activation
+	-			C3b/iC3b/C3c	Ongoing local C3 activation AND/OR C3c from local and/or systemic complement activation
-	+			C3dg	Previous local activation
+		+		C3b/iC3b (or local C3c)	Ongoing local C3 activation
+		-		C3c	Systemic complement activation
-		+		C3dg	Previous local activation
	+	+		C3dg	Previous local activation
	-	+		C3b/iC3b (or local C3c)	Ongoing local C3 activation

MPGN, nykyaikainen jaottelu patogeneesin perusteella, Lionaki et al. 2016

Klassisen tien aktivaatio → Ig-MPGN

Oikotien aktivaatio → C-MPGN eli C3G (C3GN tai DDD)

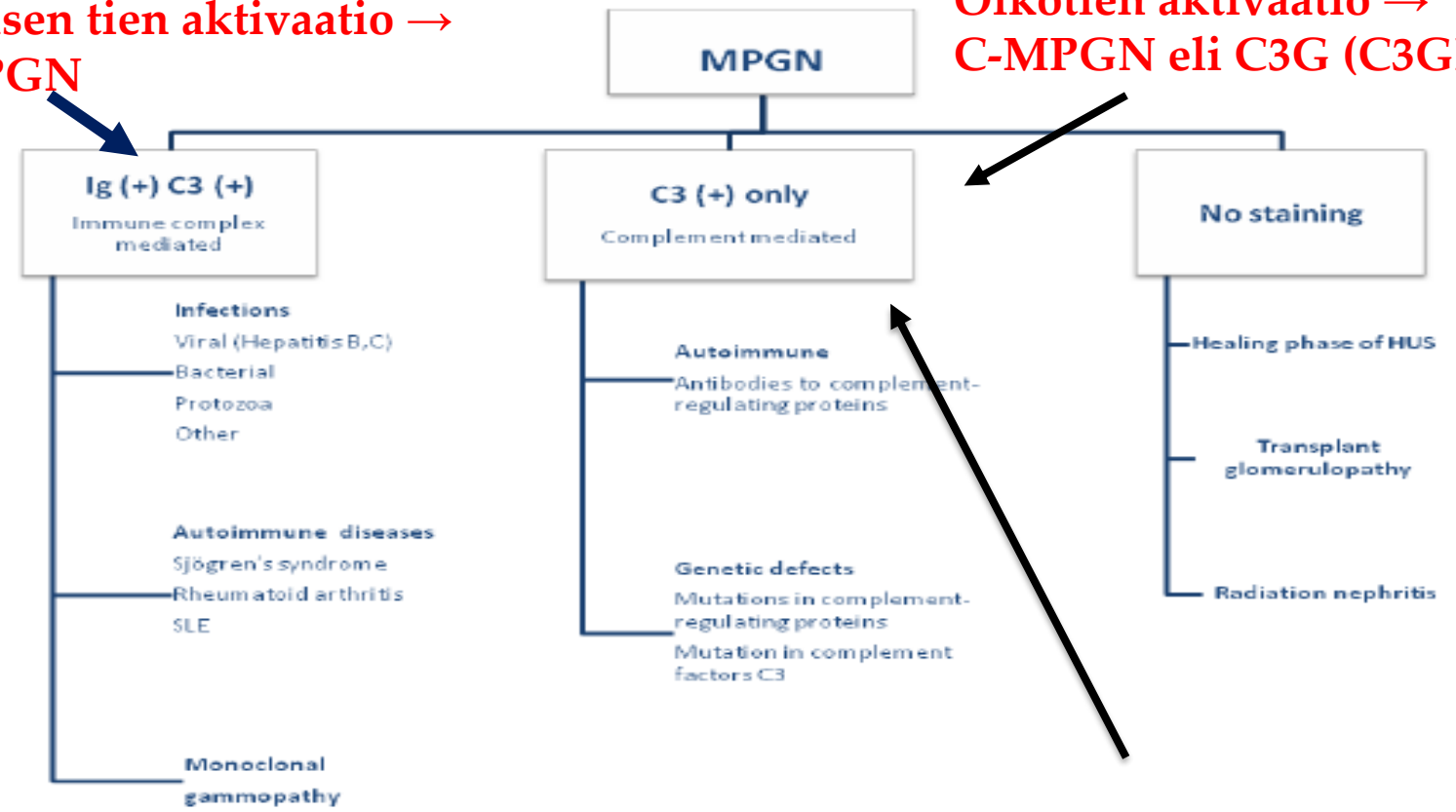
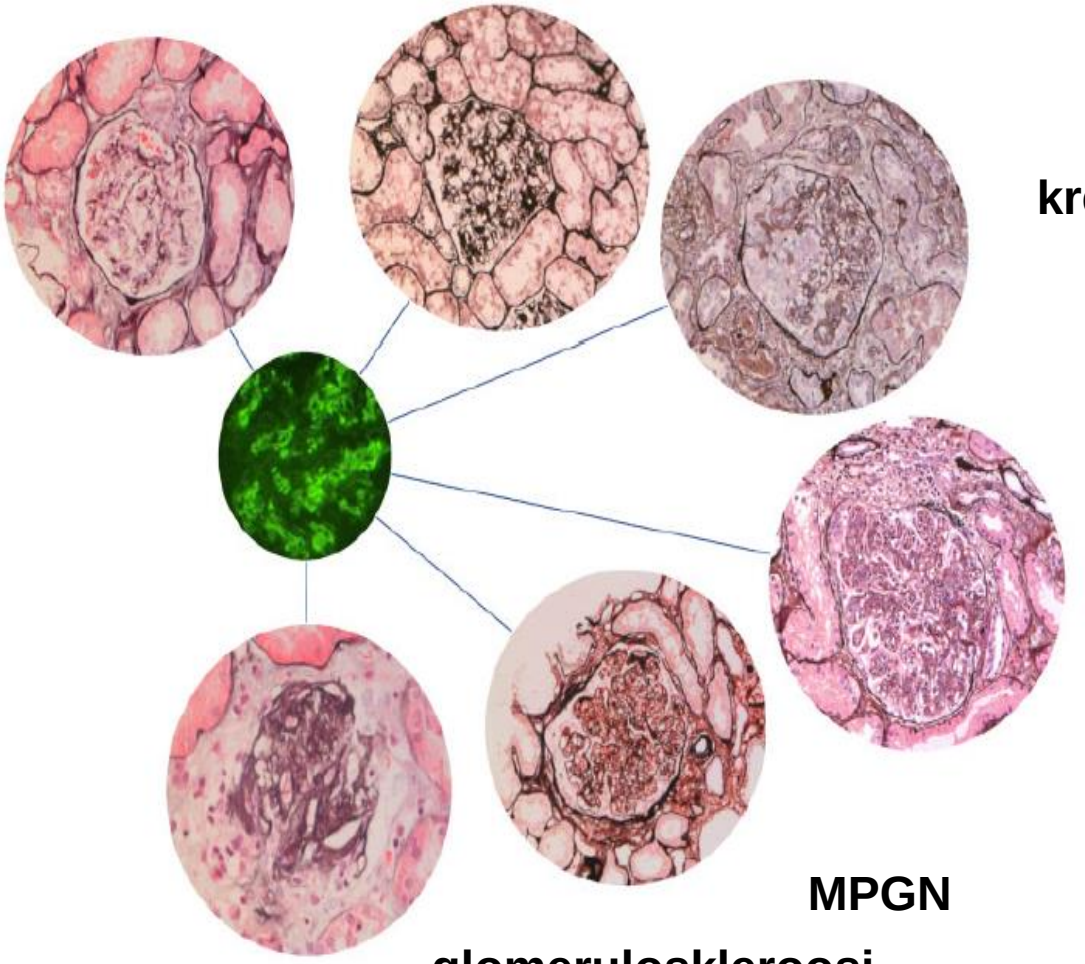


Fig. 1. Classification of MPGN according to pathogenesis.

Monoklonaalinen gammopatia, Meri et al. 1992

Obs ! Noin 20 %:lla Ig-MPGN-potilaista on kuitenkin oikotien säätelyssä häiriö, Zhao et al. 2018, Iatropoulos et al. 2018

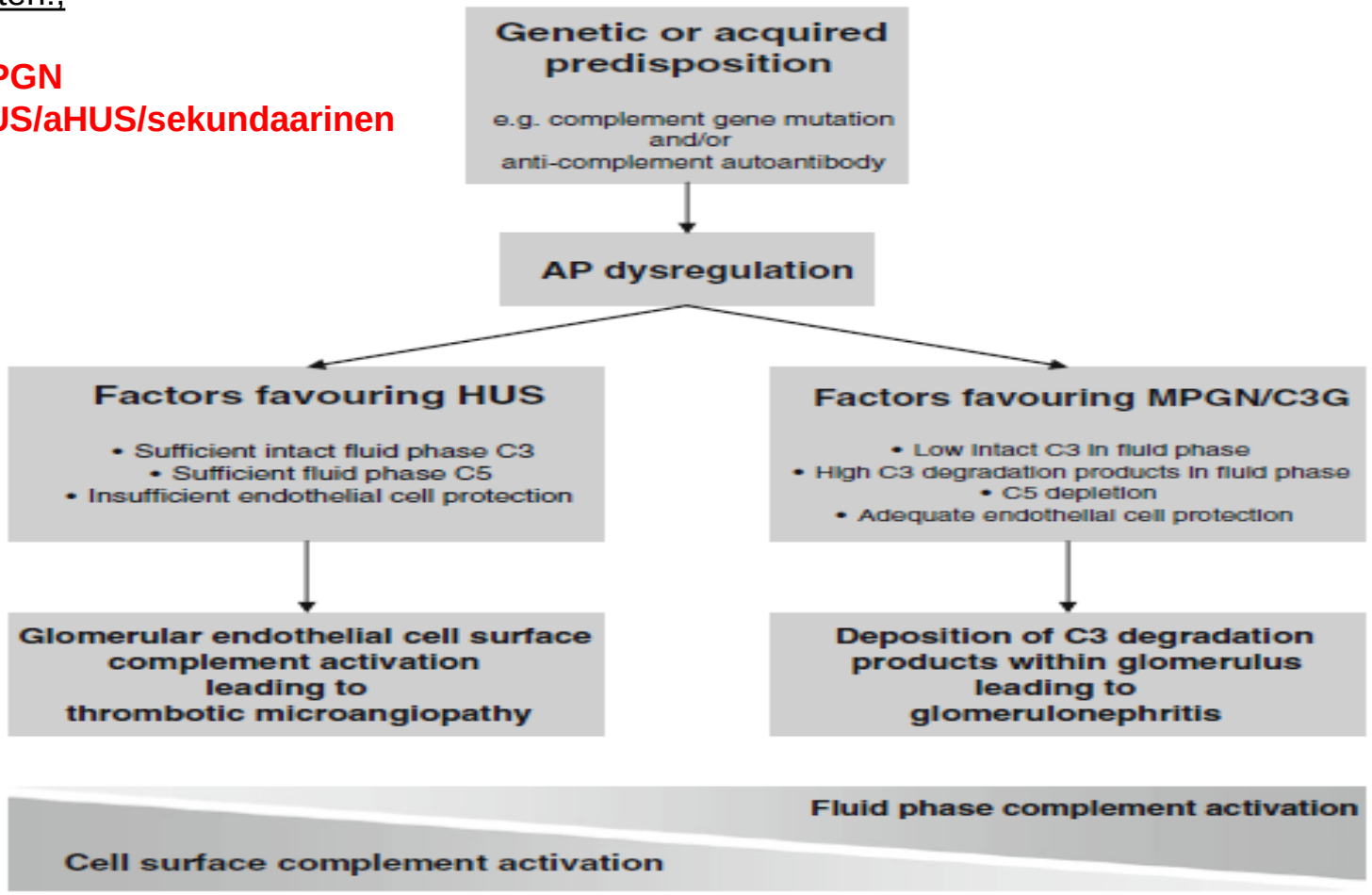
C3G – VM löydös voi olla vaihteleva, Koopman et al. 2019



aHUS, MPGN (C3GN, DDD) – kaikissa oikotien säätelyhäiriö, Johnson et al. 2014

Munuaistautirekisteri:,

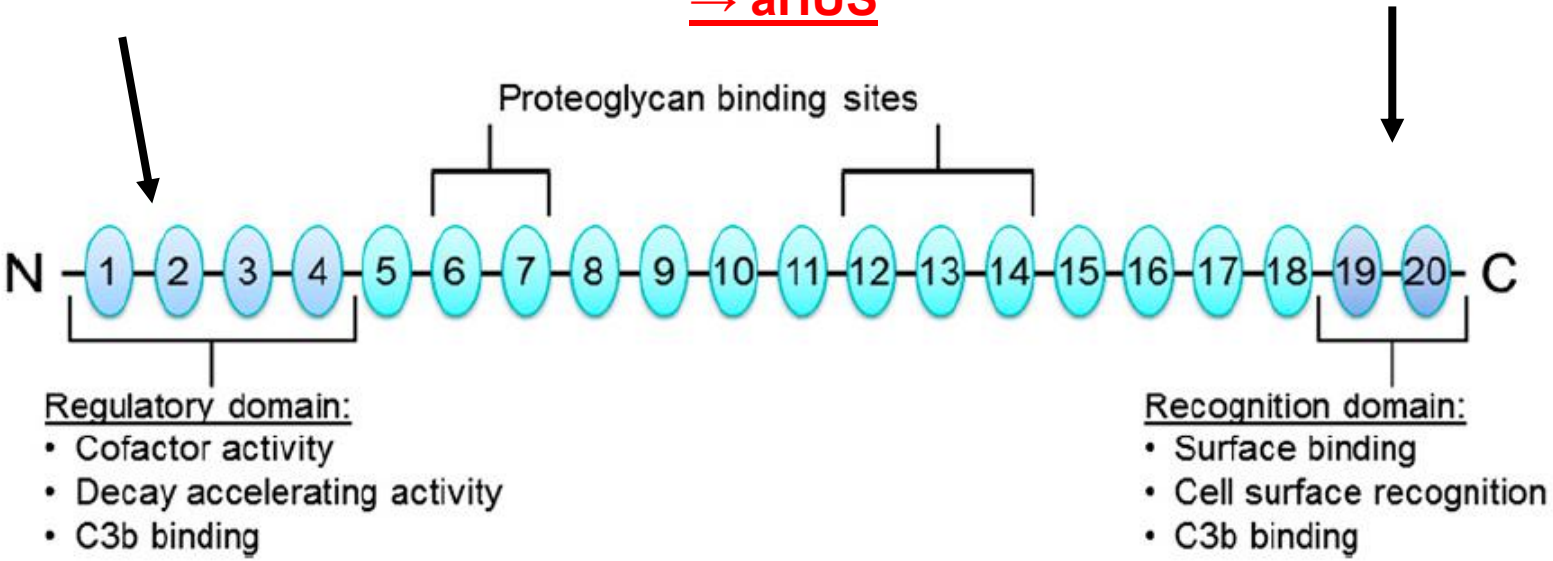
1990-2011: **85 MPGN**
1965-2015: **17 HUS/aHUS/sekundaarinen HUS, 11 TTP**



Faktori H- mutaation paikka vaikuttaa taudin fenotyyppiin, De Vriese et al. 2015

Nesteisen tilan komplementin dysregulaatio → proliferatiivinen gn

Sitoutuminen solujen pinnalle ja kudoksiin ja ligandien tunnistaminen, ts. erottelu self vs. non-self pielessä → aHUS



Faktori H ja FHR-proteiinit, De Vriese et al. 2015

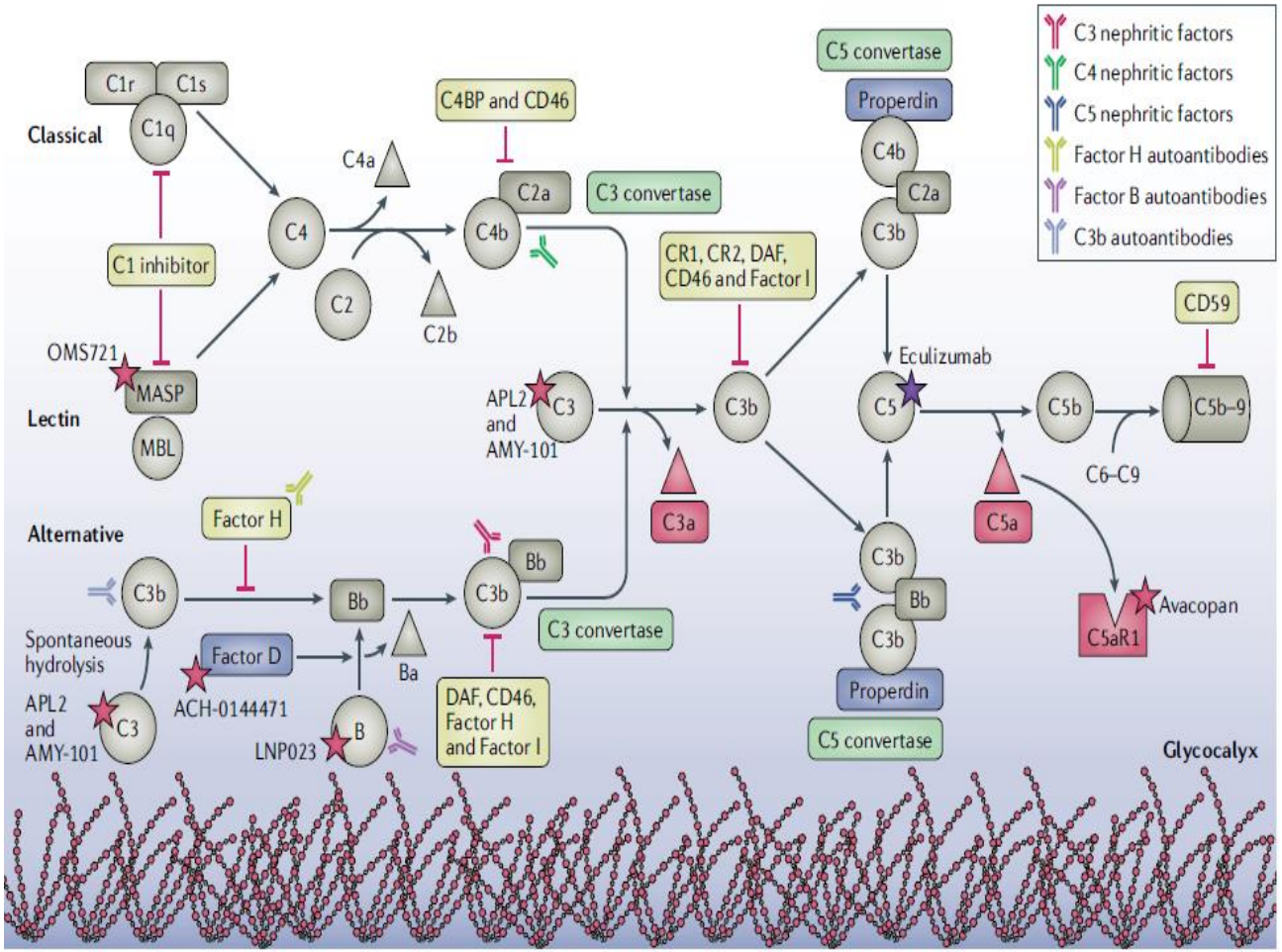
Table 1. Examples of variable phenotypic expression of CFH mutations

Mutation in CFH	Phenotypical Expression
Prol621Thr	Patient with C3 glomerulopathy later develops aHUS
Tyr899Stop	Patient with aHUS develops C3 glomerulopathy in transplant kidney
Ala161Ser; Arg1210Val; Arg53Cys	Identified in patients with aHUS and C3 glomerulopathy
Asn1117Ser	Crescentic and necrotizing GN in the region where aHUS mutations cluster

Table 2. Overview of mutations in CFHR protein genes

Genetic Defect	Phenotypical Expression	Systemic C3 Levels
Duplication in the CFHR5 gene	C3 glomerulopathy (CFHR5 nephropathy)	Normal
Duplication in the CFHR1 gene	C3 glomerulopathy	Mildly decreased
Hybrid CFHR3/CFHR1 gene	C3 glomerulopathy	Normal
Hybrid CFHR2/CFHR5 gene	C3 glomerulopathy	Decreased
Hybrid CFH/CFHR1 gene	aHUS	Mildly decreased or normal
Hybrid CFH/CFHR3 gene	aHUS	Normal
Mutation in the CFHR5 gene	Atypical postinfectious GN	Decreased

C3G-taudin monimuotoiset autoimmuunitaustat, Smith et al. 2019



> 90 % potilaista häiriö on oikotiessä,
< 10 % potilaista häiriö on klassisen tai lektiinitien alueella

Table 5 | **Novel therapeutic agents that target complement activity**

Drug	Target	Mechanism	Clinical trial number
ACH0144471	Factor D	Prevents formation of C3 and C5 convertases	NCT03369236, NCT03459443 and NCT03124368
LNP023	Factor B	Prevents formation of C3 and C5 convertases	Not yet registered
APL2	C3	Prevents formation of C3 and C5 convertases	NCT03453619
AMY101	C3	Prevents formation of C3 and C5 convertases	NCT03316521
OMS721	MASP2	Blocks initiation of lectin pathway	NCT02682407
Eculizumab	C5	Blocks progression of terminal pathway	Off-label use
Avacopan	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT03301467

No clinical trials of drugs that enhance complement regulation are currently ongoing in patients with C3 glomerulopathy.

C3G-taudin monimuotoiset autoimmuunitaustat, Smith et al. 2019

Table 4 | Acquired drivers of C3 glomerulopathy

Driver	Frequency in affected patients (%)	Function	Knowledge gaps	Refs
C3 nephritic factors	50–80	Dysregulation of C3 convertase (C3bBb)	• Diagnostic assays need standardization • In vitro function of antibodies is well characterized; however, well-documented in vivo data supporting cause-and-effect relationships to disease are needed • Not known whether antibody characteristics change over the disease course • Unclear why antibody removal methods (plasma exchange or B cell-targeted agents) are generally not effective • Defining the mechanism underlying complement dysregulation is often very difficult	60
C4 nephritic factors	2.4	Dysregulation of C3 and C5 convertases of the classical and lectin pathways (C4b2a and C4b2aC3b)		60
C5 nephritic factors	50	Dysregulation of C5 convertase (C3bBbC3b)		57
Factor H autoantibodies	~1.0	Affects factor I cofactor activity; not associated with *CFHR3* or *CFHR1* gene deletion		58
Factor B autoantibodies	~2.5	Recognizes the Bb fragment; binds C3 convertase; increases release of C3a and Bb; does not enhance C5 convertase activity		59
C3b autoantibodies	1.5	Recognizes C3b and C3c; stabilizes C3 convertase; reduces binding to complement receptor type 1; increases activity of C5 convertase		59
Monoclonal immunoglobulins	Sporadic cases of multiple myeloma or MGRS	Intact antibody and/or light-chain fragments interfere with alternative pathway regulation		65,70,71

MGRS, monoclonal gammopathy of renal significance.

C3G-taudin taustat, kun mukana myös todetut mutaatiot, Bomback et al. 2018, Goodship et al. 2017

	C3GN (N=42)	DDD (N=9)
(A) Complement-associated genetic variants		
C3	2 (4.8%)	0 (0.0%)
CFH	8 (19.0%)*	3 (33.3%)
CFI	0 (0.0%)	0 (0.0%)
CFB	0 (0.0%)	0 (0.0%)
CFHR5	1 (2.4%)	0 (0.0%)
MCP	1 (2.4%)	0 (0.0%)
(B) Complement-associated autoantibodies		
C3Nef	13 (31.0 %)	1 (11.1%)
Factor H Ab	3 (7.1%)	1 (11.1%)
Factor B Ab	0 (0.0%)	0 (0.0%)

Genes associated with aHUS and C3G

Complement genes

- Complement Factor H (*CFH*)
- Complement Factor H-related genes 1 to 5 (*CFHR1-5*)
- Membrane cofactor protein (*MCP*)
- Complement Factor I (*CFI*)
- Complement Factor B (*CFB*)
- Complement Component 3 (*C3*)

Non-complement genes

- Diacylglycerol kinase-ε (*DGKE*)

C3G prototypical genetic variants

- *CFH* pathogenic variants associated with very low FH levels
- *CFHR1*, *CFHR2* and *CFHR5* genomic rearrangements leading to the expression of fusion proteins typically resulting in duplication of the FHR-1, FHR-2 and FHR-5 dimerization domains (SCRs 1 and 2)
- Increased copy numbers of some *CFHR1-5* genes (especially *CFHR1*)
- C3 pathogenic variants (i.e., p.D923G924del and p.I756T)
- *CFH-H1*, MCP_{aaggt} C3G risk haplotypes
- *CFHR5*-p.P46S C3G risk allele

Sekä C3- että C5- välitteinen vaurio aiheuttavat ongelmia C3G-taudissa, Barbour et al. 2013

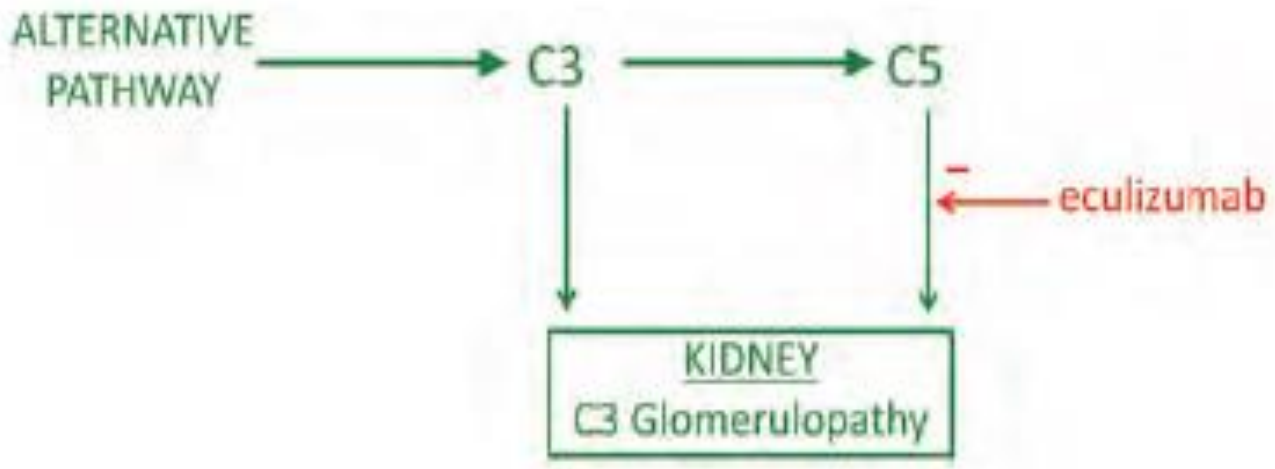
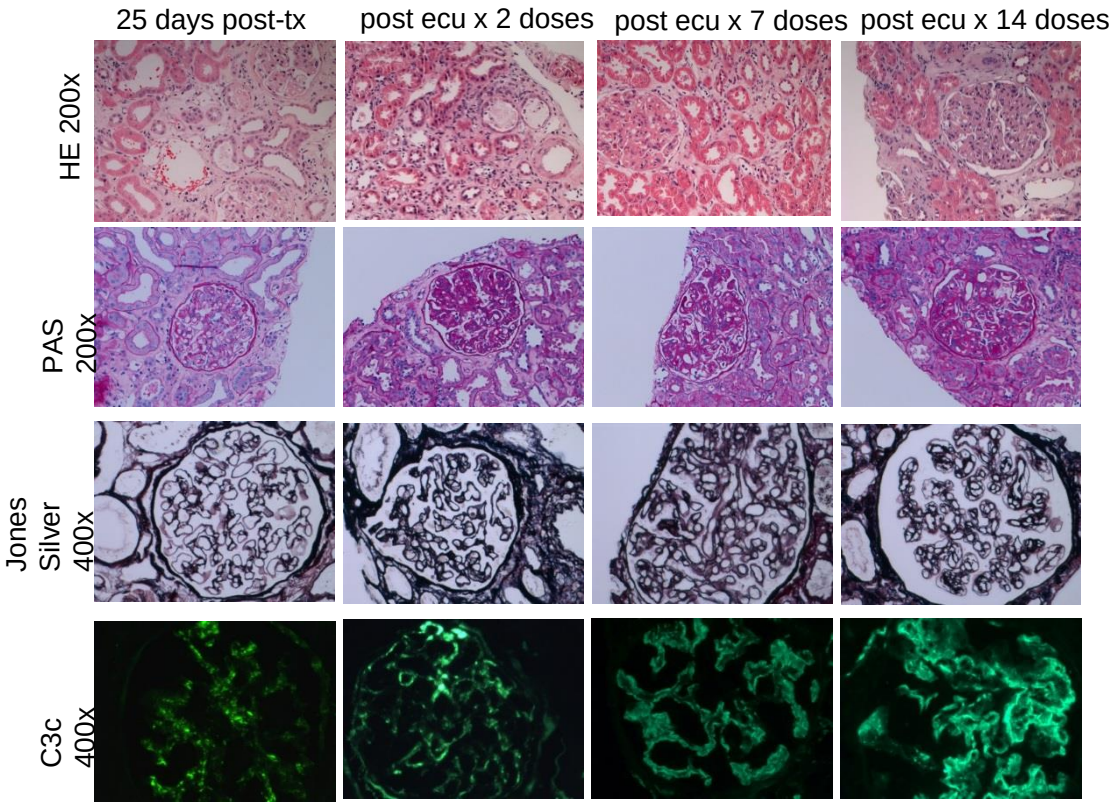


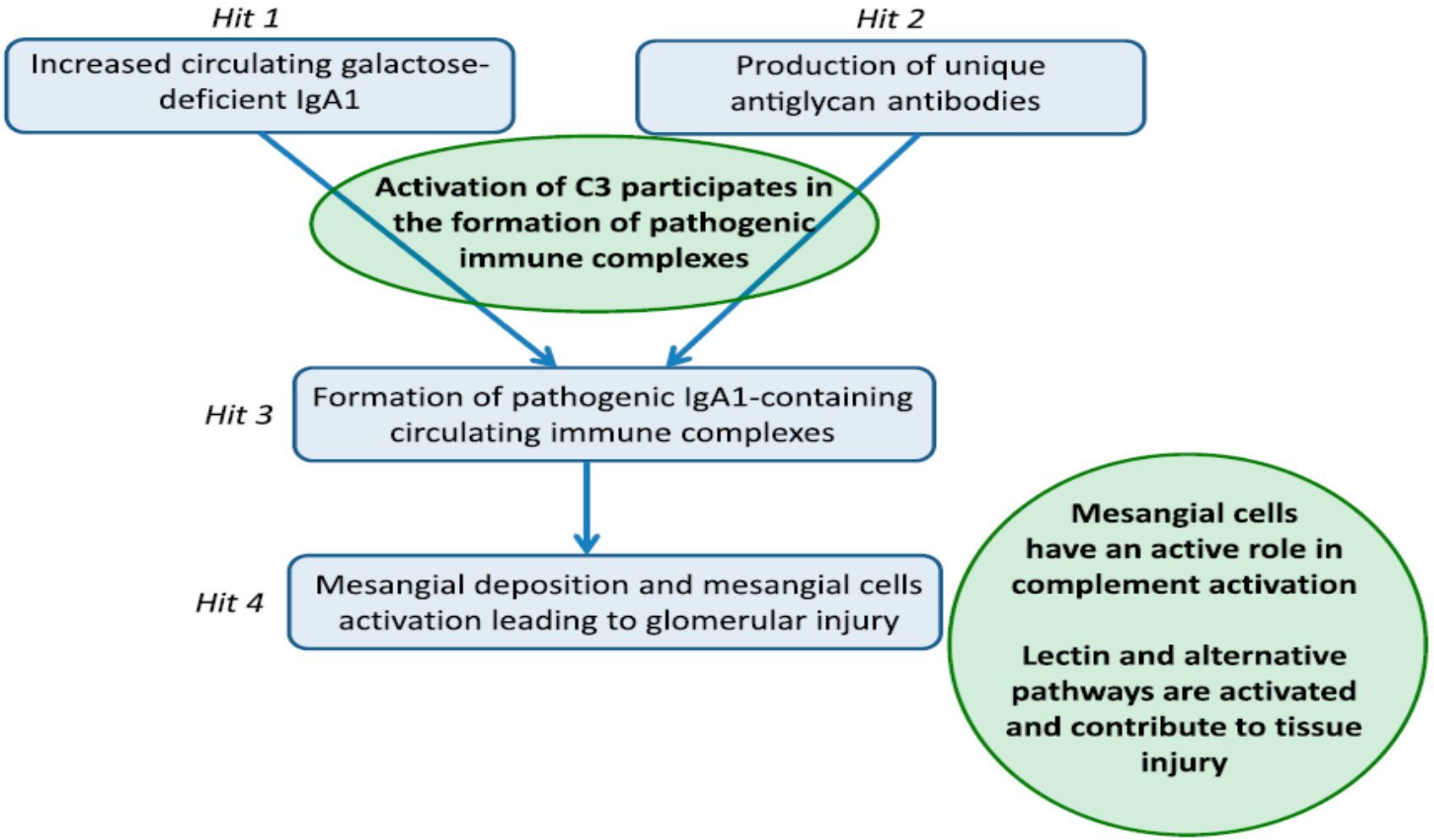
FIGURE 3: Therapeutic complement blockade in C3GN.

C3nef analyysi voisi auttaa näiden kahden vauriomekanismin selvittelyssä ? Kaartinen et al. 2017

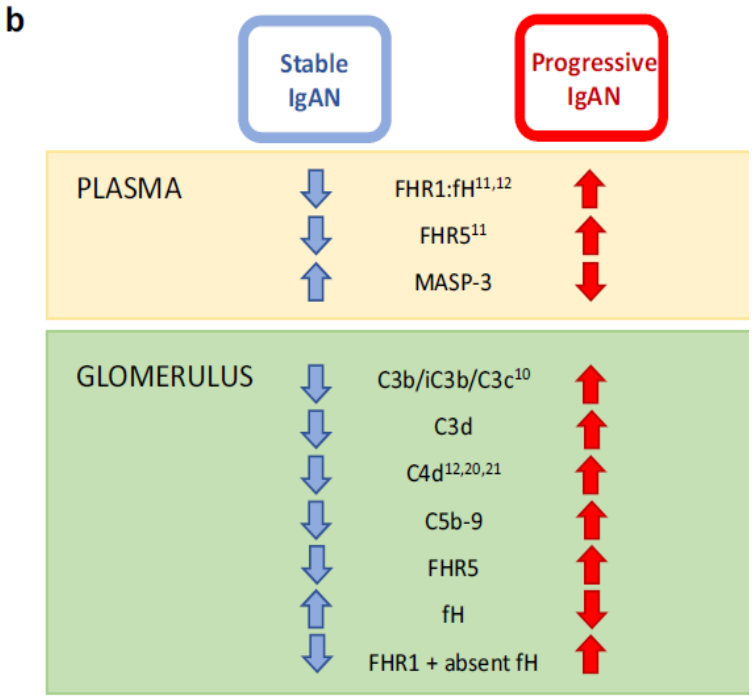
..jonka vuoksi C5-estäjä ei autakaan..C3GN ja ekulitsumabi-hoito, Kaartinen et al. 2017

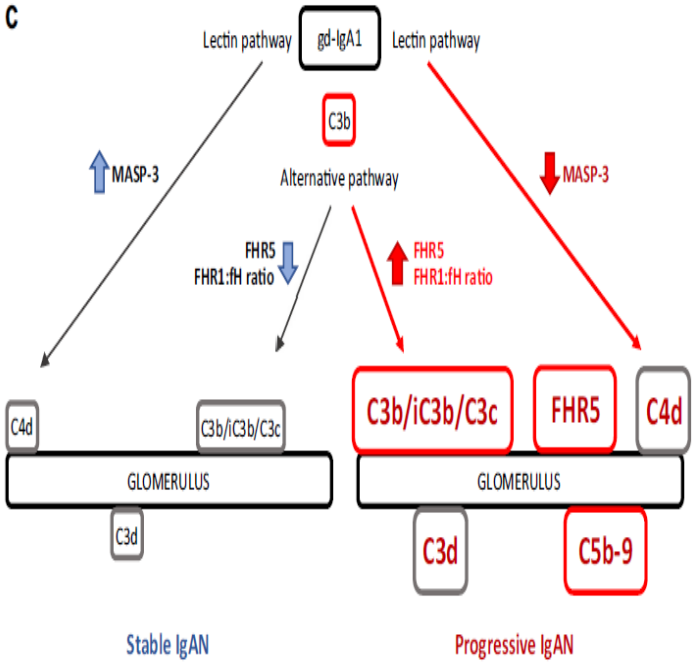


IgAGN syntymekanismi ja komplementin osuus, Maillard et al. 2015



Komplementtiprofiili ennustaa IgAGN-taudin käyttäytymistä, Medjeral-Thomas et al. 2018





Komplementti ja IgAGN, mitä tiedetään I ?

- **FHR1- ja FHR3-deleetiot** vaikuttivat suojaavan IgA nefropatialta, Gharavi et al. 2011
  - 4 kohorttia yhdistettynä (kiinalainen x2, amerikkalainen, eurooppalainen), 3200 pot
  - ..lisää kyllä SLE ja anti H aHUS-riskiä..(Zipfel et al. 2019)
- Sekä **seerumin matala C3 että korkeampi mesangiumin C3** ennustivat itsenäisesti taudin progressiota, Kim et al. 2012
  - Retrospektiivinen, havainnoiva kohorttitutkimus, 343 pot, 19 % oli madaltunut s-C3, f-u 53 kk
- **Seerumin matala C3/C4 suhde** ennusti nopeaa munuaistoiminnan menetystä, Pan et al.2018
  - Retrospektiivinen työ, 712 pot, f-u 41 kk,
- Plasman **FHR1 ja FHR1/fH-suhde** ovat koholla ja assosioituivat progressiiviseen tautiin, sen sijaan FHR5 tai FHR5/fH-suhde eivät assosioituneet progressiiviseen tautiin, Medjeral-Thomas et al. 2017
  - Retrospektiivinen, 179 progressiivista + 89 stabiilia pot, 161 tervettä verrokkia, f-u 55 kk
- Korkeampi **plasman FHR1-taso** ennusti itsenäisesti progressiivista tautia, Tortajada et al. 2017
  - Retrospektiivinen kohorttitutkimus, 112 pot, f-u 77 kk,

Komplementti ja IgAGN, mitä tiedetään II ?

- Sekä mannoosia sitovan lektiinin (**MBL**) puute että ylimäärä assosioituvat huonompaan ennusteeseen, Guo et al. 2017
  - Retrospektiivinen, 749 pot, 489 tervettä kontrollia, f-u 47 kk,
- FHR1, 3-deleetiot eivät ennustaneet filtraation heikentymistä, mutta linkittyivät vähäisempään mesangiaaliseen C3-kertymään, Jullien et al. 2018
  - Retrospektiivinen, 639 pot, f-u 132 kk,
- Plasman **FHR5 -tasot** olivat korkeampia kuin terveillä verrokeilla ja korkeampi taso ennusti nopeampaa munuaistoiminnan menetystä, Zhu et al. 2018
  - RETRO ?? 1126 pot, 153 verrokkia, f-u 44 kk,
- **Veren matalat MASP-3 ja FHR5-kertymät** histologiassa ennustivat progressiivista tautia, Medjeral-Thomas et al. 2018
  - Retrospektiivinen, 323 pot, f-u 55 kk
- **Mesangiaalinen C3 (≥ 2 vs. < 2) ja C4d (pos. vs. neg)** kertymät ennustivat itsenäisesti munuaisfunktion heikentymistä, Nam et al. 2020
  - Retrospektiivinen, 380 pot, f-u 8v

Kiitos !

…but at least you can get confused on a higher level…