Thérapeutiques ciblant le complément

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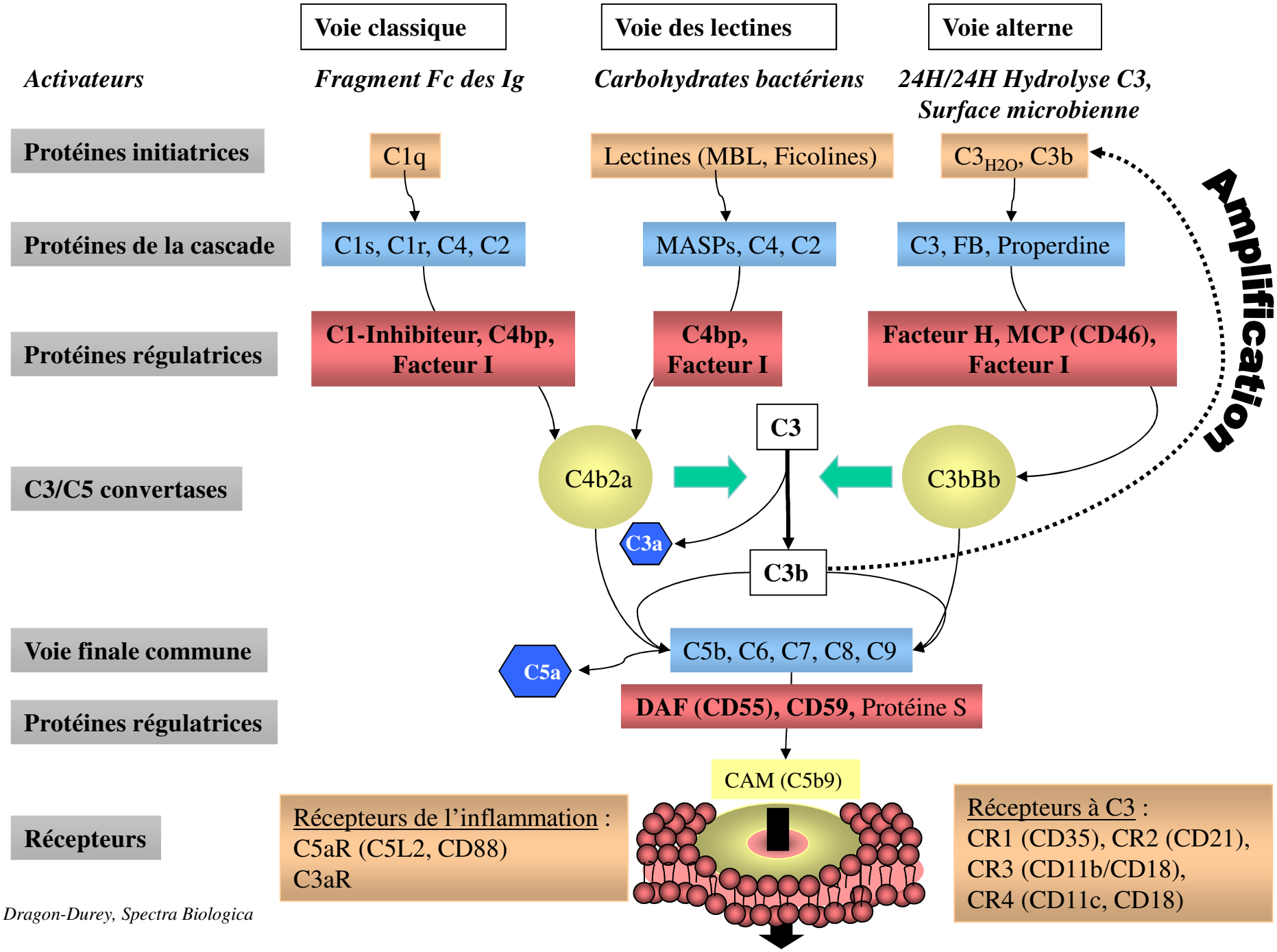
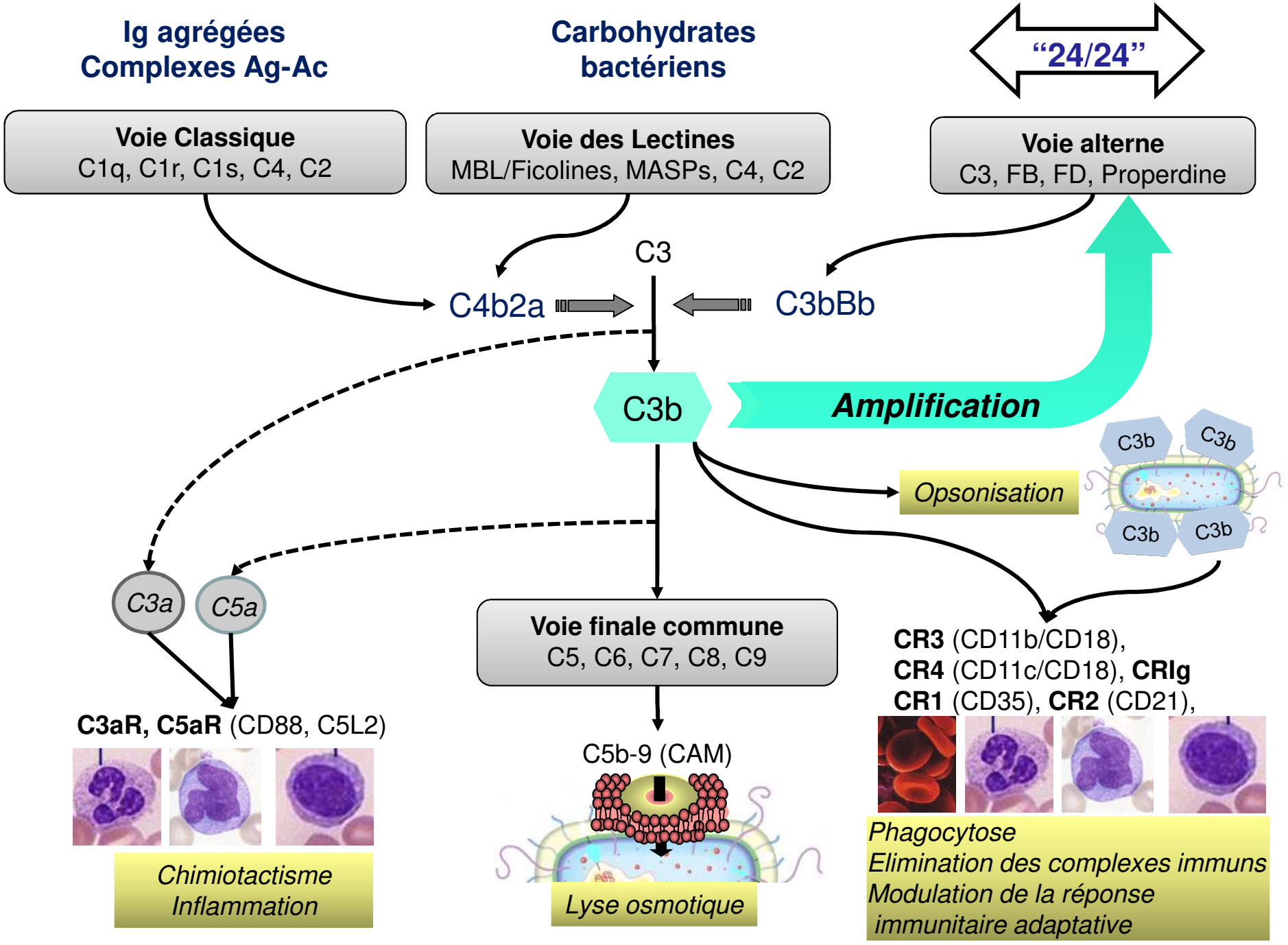
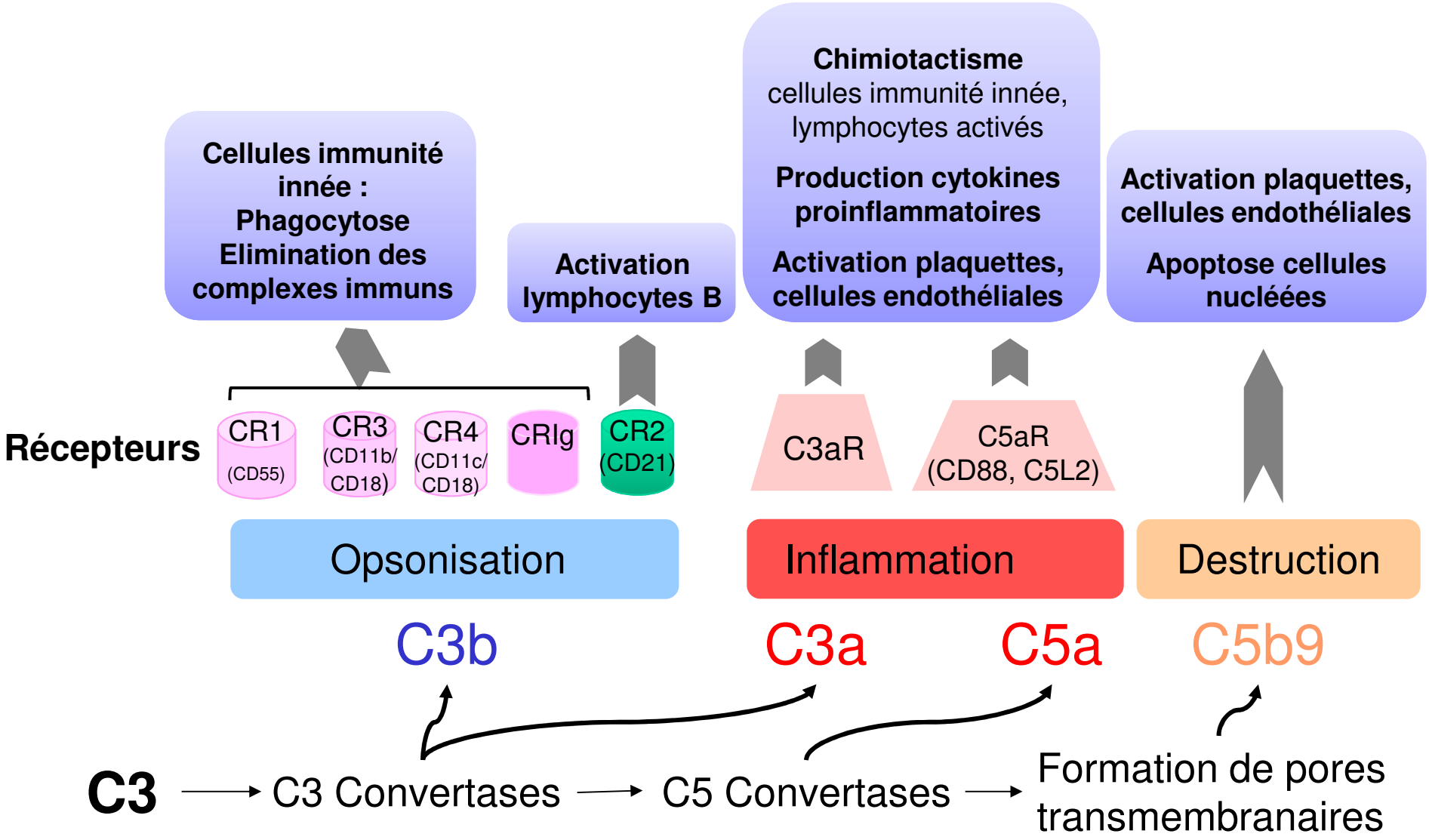


Dragon-Durey, Spectra Biologica


Ig agrégées
Complexes Ag-Ac
Carbohydrates
bactériens
"24/24"
Voie Classique
C1q, C1r, C1s, C4, C2
Voie des Lectines
MBL/Ficolines, MASPs, C4, C2
Voie alterne
C3, FB, FD, Properdine
C3
C4b2a
C3bBb
C3b
Amplification
C3b
C3b
C3b
C3b
Opsonisation
C3a
C5a
Voie finale commune
C5, C6, C7, C8, C9
CR3 (CD11b/CD18),
CR4 (CD11c/CD18), CRIg
CR1 (CD35), CR2 (CD21),
C3aR, C5aR (CD88, C5L2)
C5b-9 (CAM)
Chimiotactisme
Inflammation
Lyse osmotique
Phagocytose
Elimination des complexes immuns
Modulation de la réponse
immunitaire adaptative

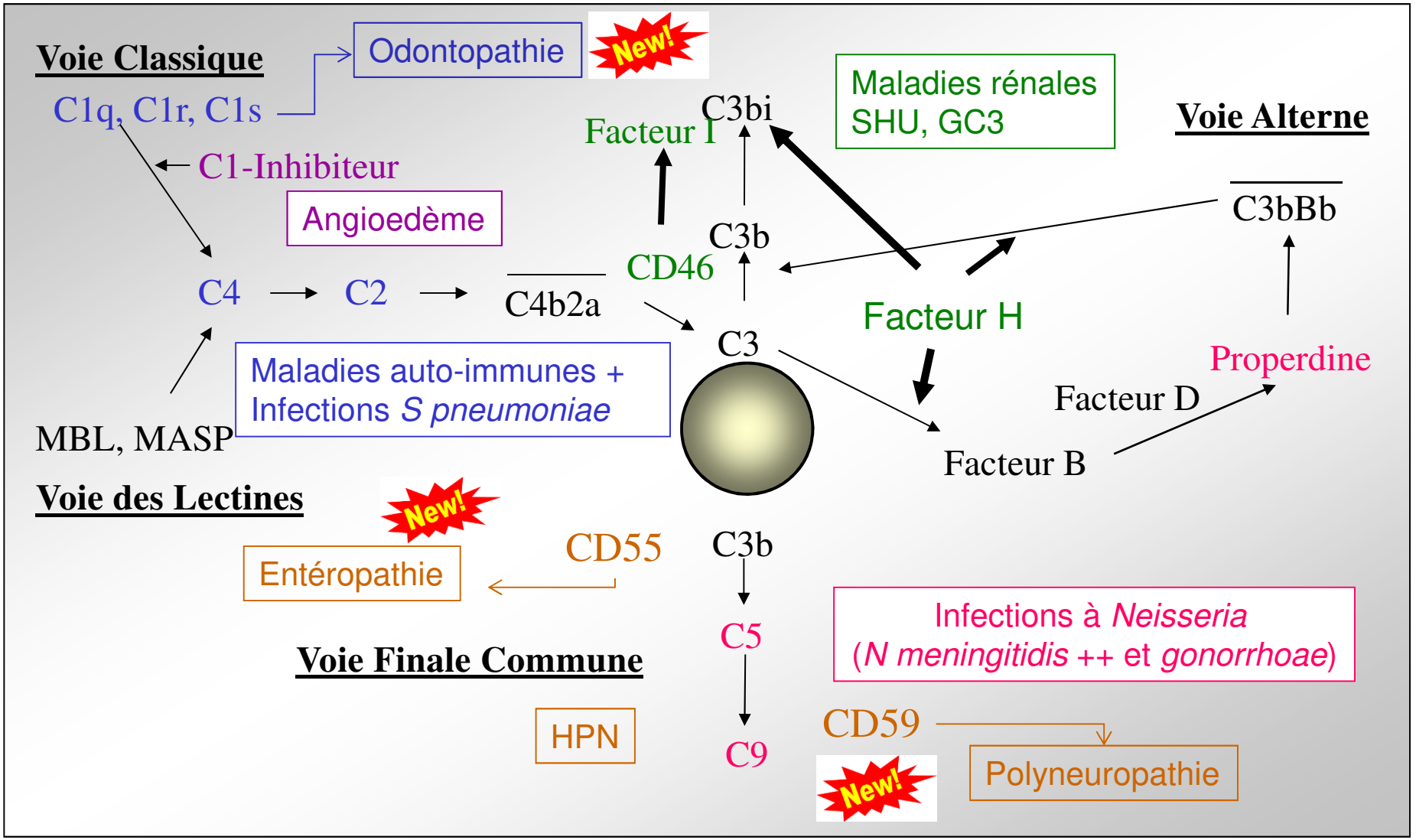
Complément et modulation de la réponse immunitaire



Complément et pathologies humaines

- Déficits en protéines du complément : association avec des pathologies diverses
- Protéines du Complément : cibles d'auto-anticorps
- Rôle dans l'inflammation : participation aux lésions tissulaires : maladies autoimmunes (reins et LED), ischémie-reperfusion, choc septique…
- Cible de nouvelles thérapeutiques

Déficits en protéines du Complément et pathologies

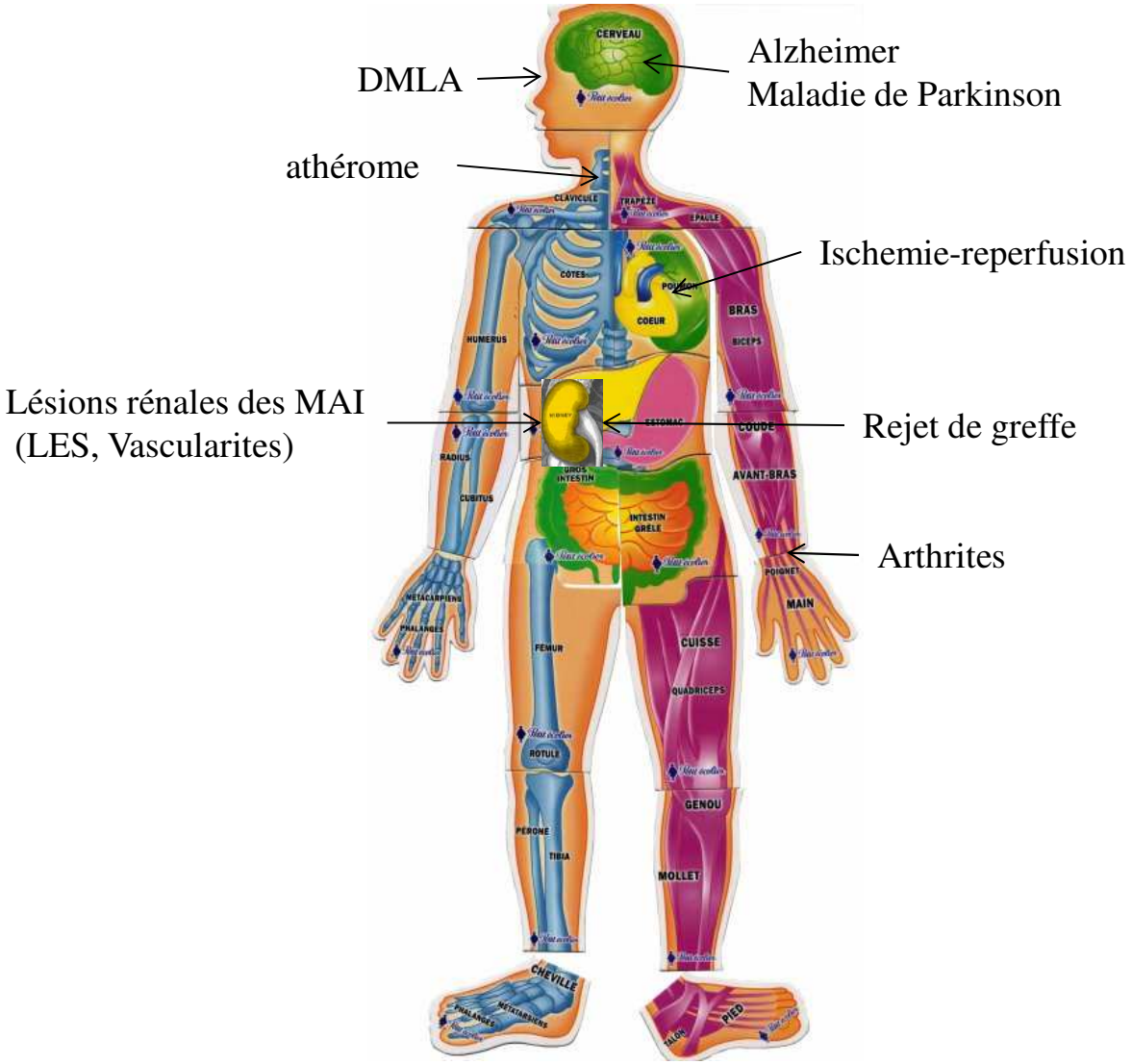


Mécanismes physiopathologiques associés aux déficits en protéines du Complément

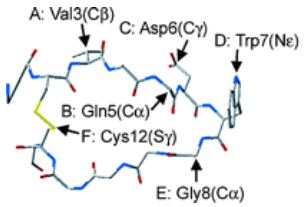
Déficits touchant les composants de la cascade :
Phénotype lié à un *défaut de fonction* du système du Complément :
-Elimination des CIC,
-Elimination des pathogènes

Déficits touchant les régulateurs de la cascade :
Phénotype lié à une *suractivation du système du Complément :*
-Activation cellulaire (¢ endothéliales, Plaquettes, Lymphocytes, macrophages),
-dépôts tissulaires (C3b, C5b9),
-destructions cellulaires (¢ endothéliales, axones..)

Complément et pathologies humaines



Complément : cible de nouvelles thérapeutiques



Anti-MASP

C1-Inhibiteur

-OAN
-Prévention de lésions ischémie/reperfusion
-Syndrome de fuite capillaire

sCR1 : TP10,
Chim CD46-CD55 : CAB-2
anti-C3 et C5 convertase
CR2-FH , CR2-Crry
Anti-FB, mini-FH

C3 convertase classique

C3

C3 convertase alterne

C3a

CR1
Opsonisation

C3b

Compstatin
Fixation C3

C5 convertase

Anti-C5
(pexeluzimab, **eculizumab**)

C5a

- HPN/SHU (AMM)
- Chirurgie cardiaque
- Rejet de greffe
-GNMP...

C5aR antagoniste
(CCX 168)

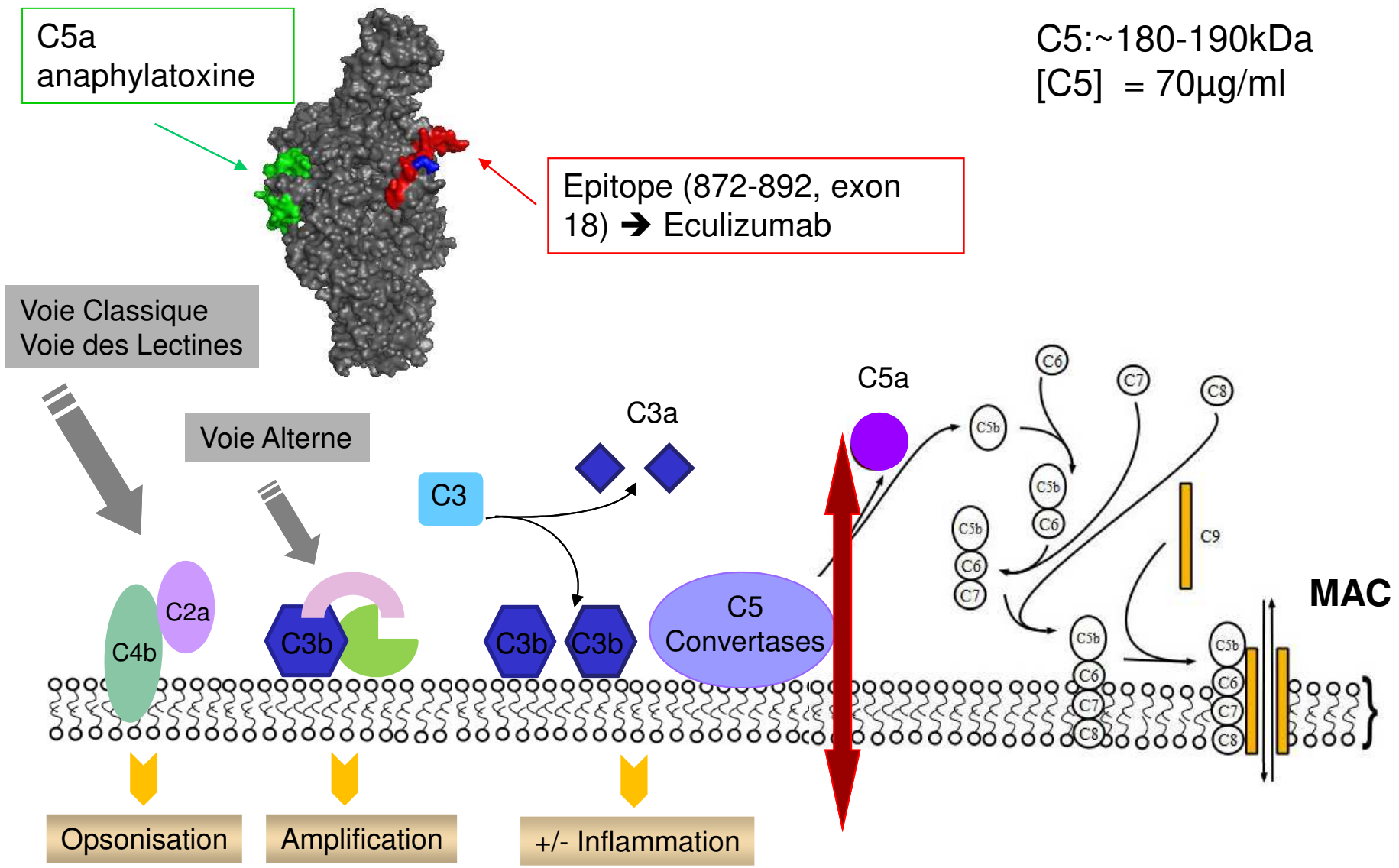
Vascularites à ANCA
(GC3, SHU)

CD59

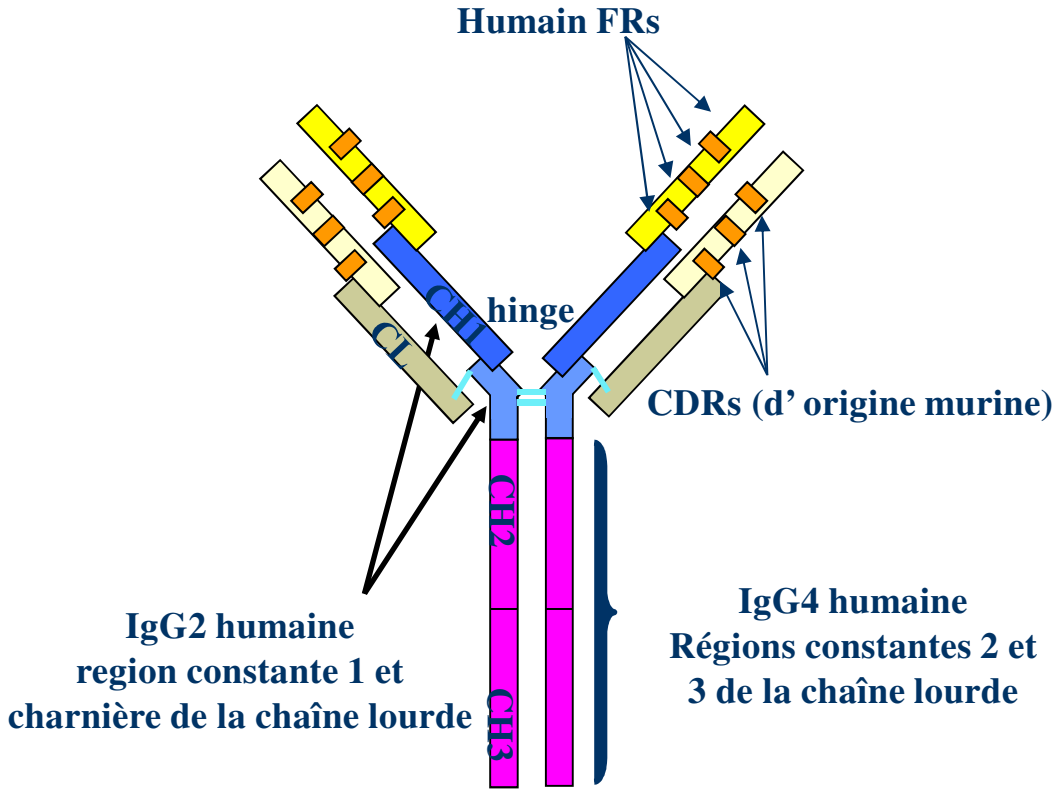
C5b9

Anti-CD59
CR2-CD59

Cibler le Complément (C5) en auto-immunité : traiter les conséquences et non la cause



Eculizumab « Soliris »: structure



Conséquences fonctionnelles :

Ne se lie pas aux RFc
N'active pas la cascade du Complément.

Blocage du clivage de C5 ➔ blocage de l'activité hémolytique du complément et de la production de C5a

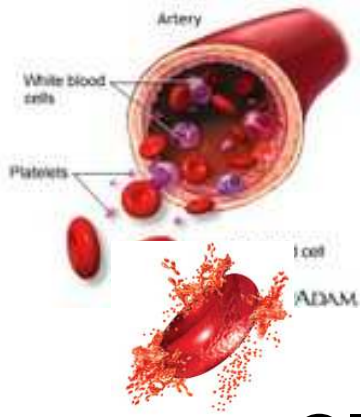
Maintien des fonctions d'opsonisation, de lutte anti-infectieuse et d'élimination des complexes immuns.

Conséquence de l'inhibition de la voie finale commune du Complément

→Susceptibilité aux infections à méningocoque

→ Vaccination obligatoire anti-méningocoques (A, C, Y, W135) + antibiothérapie prophylactique (cas de méningococcémies sous vaccination seule)

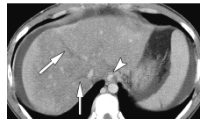
Hémoglobinurie Paroxystique Nocturne (HPN)



Anémie hémolytique acquise

Thromboses

+/- Aplasie médullaire



HPN

HPN Classique

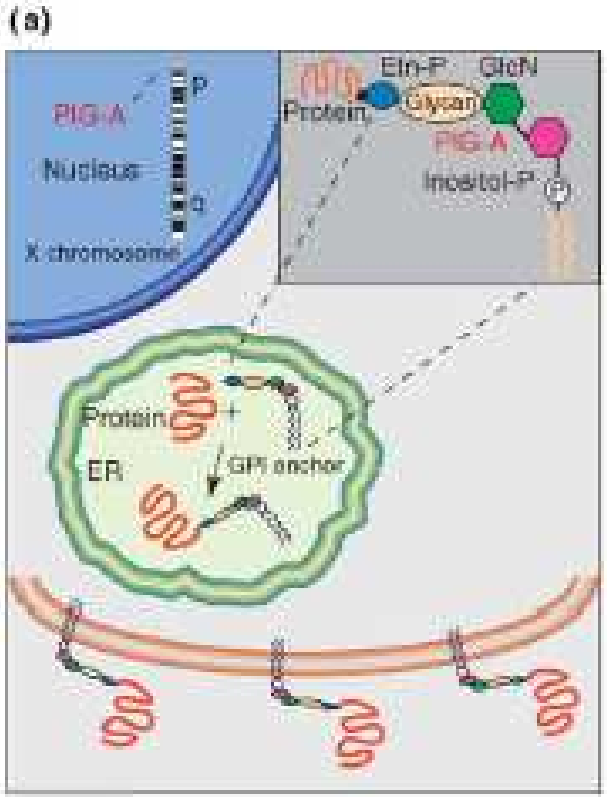
Hémolyse intra vasculaire
Moelle « normale »

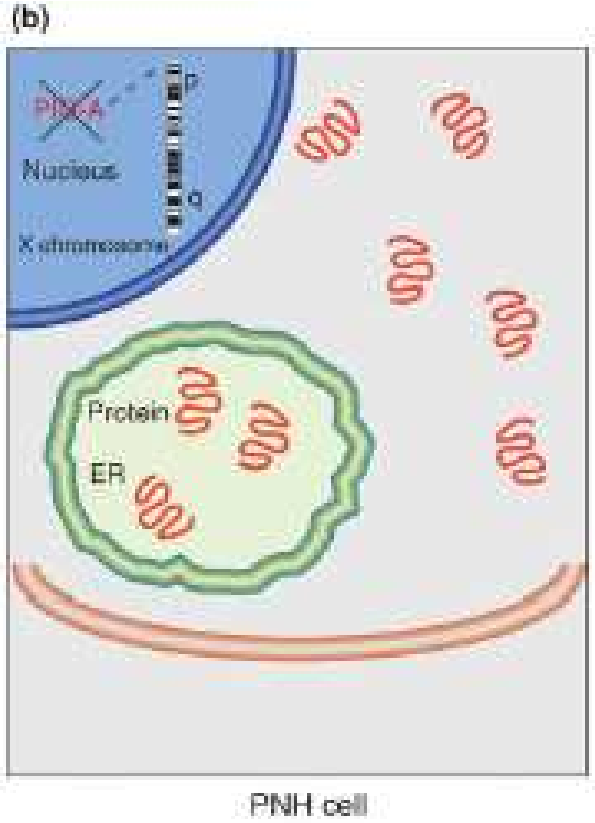
AA HPN

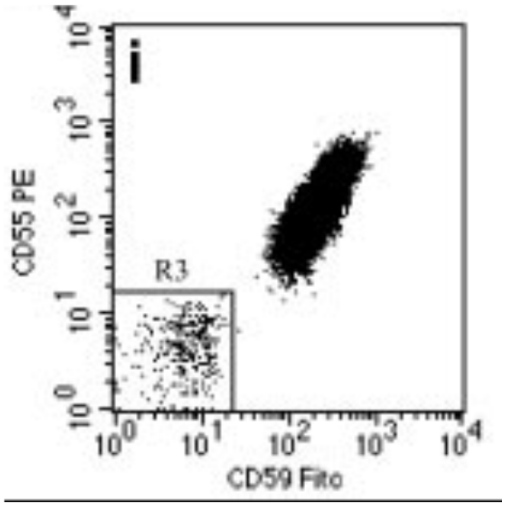
HPN et insuffisance médullaire
(AA, MDS)

- **Déficit d'expression des molécules GPI-ancrées (CD55 et CD59, CD14, LFA-3, CD16)**
- **Maladie de la Cellule Souche Hématopoïétique**
- **Mutation acquise (somatique) du gène PIG-A**
- **8000 à 10 000 patients en Amérique du Nord et en Europe**
- **Prévalence en France : 7,7 cas /million**

Hillmen P et al. *N Engl J Med.* 1995; Parker C et al. *Blood* 2005; Peffault de Latour et al. *Blood* 2008



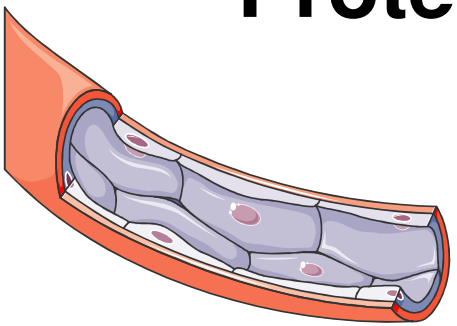


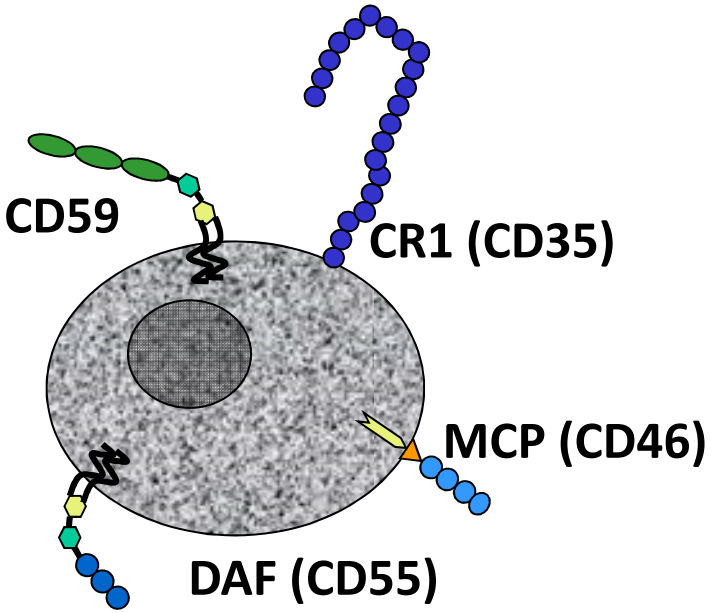


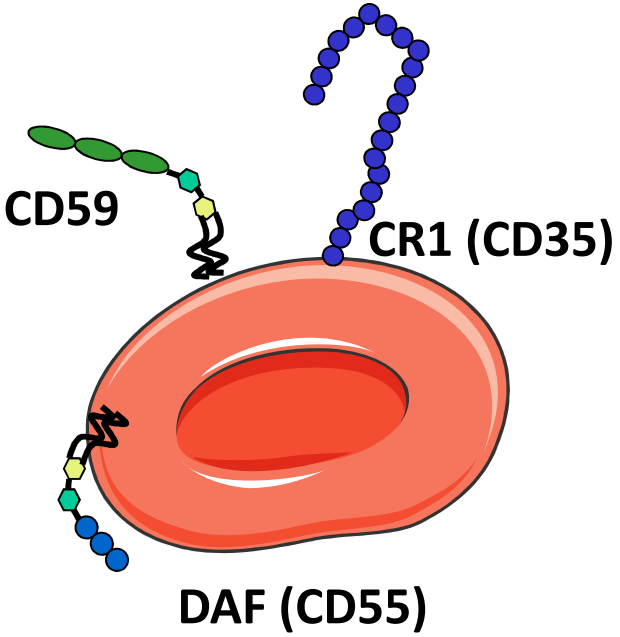
Expression CD55 et CD59

<u>CMF sur hématies</u> (d'après Parker et al, Blood, Dec 2005)

Protection restreinte des globules rouges





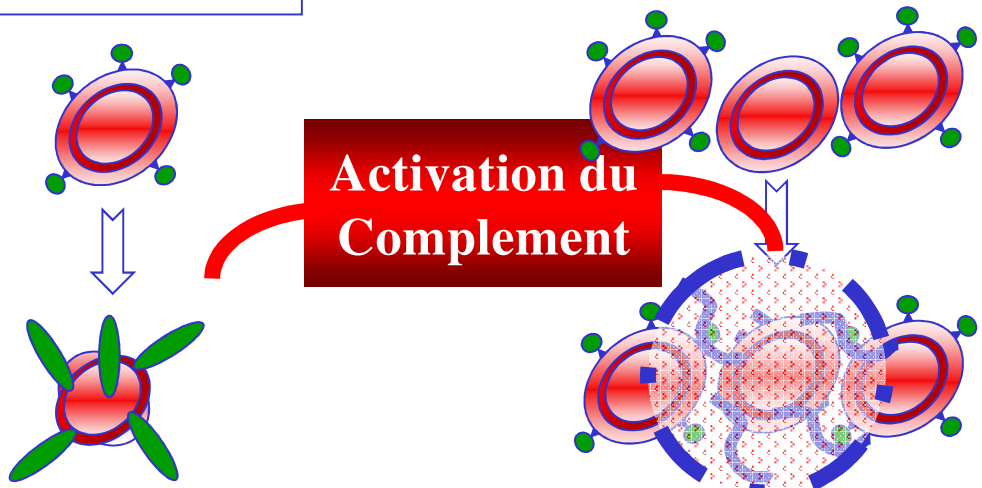


HPN clone

HPN: conséquences et signes cliniques

Les GR normaux sont protégés de l'attaque du complément par les régulateurs membranaires

Sans la présence des inhibiteurs à leur surface, les GR HPN sont lysés



Activation du Complement

GR intacts

Hémoglobinurie

Insuffisance rénale

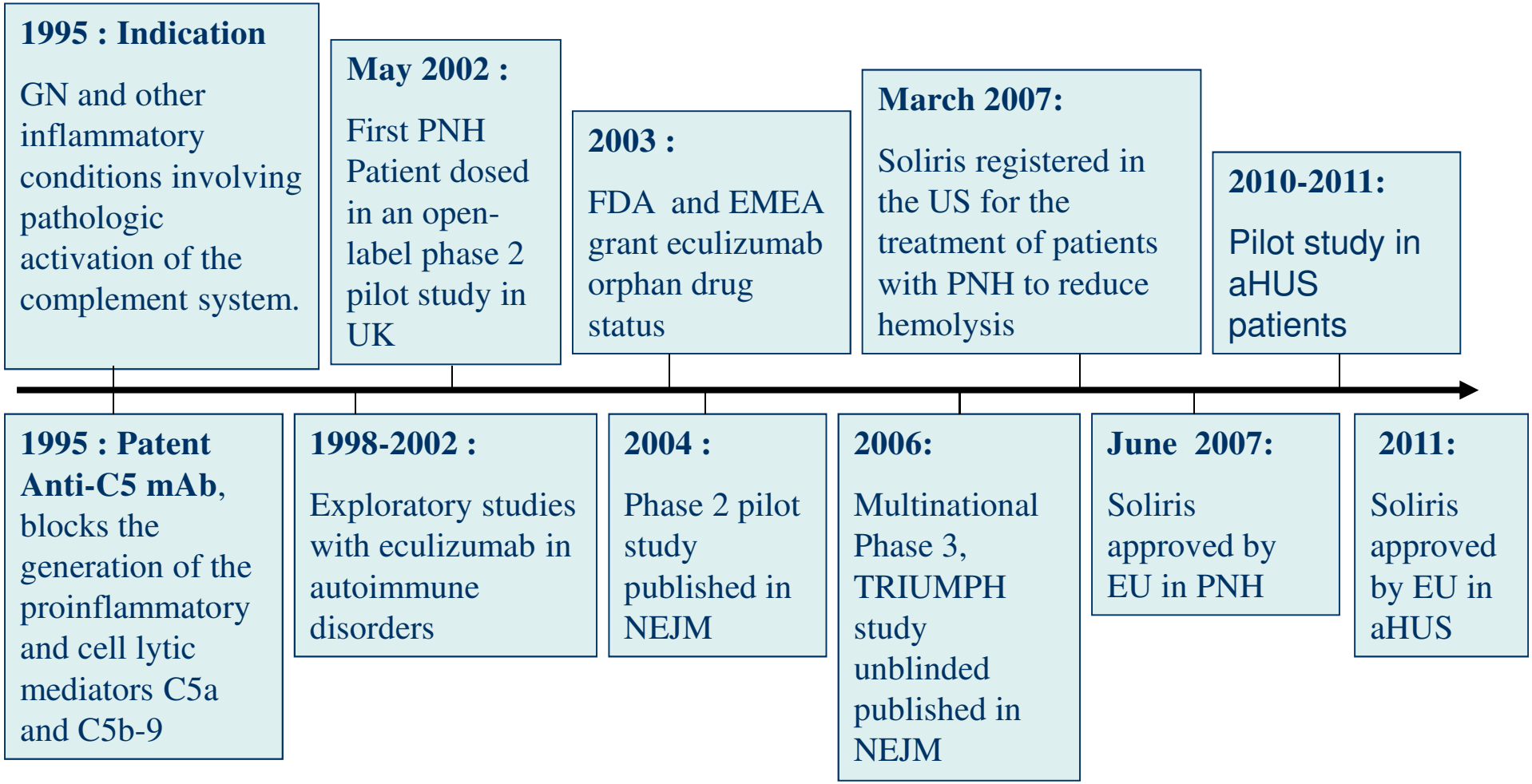
Hb libre

Fatigue

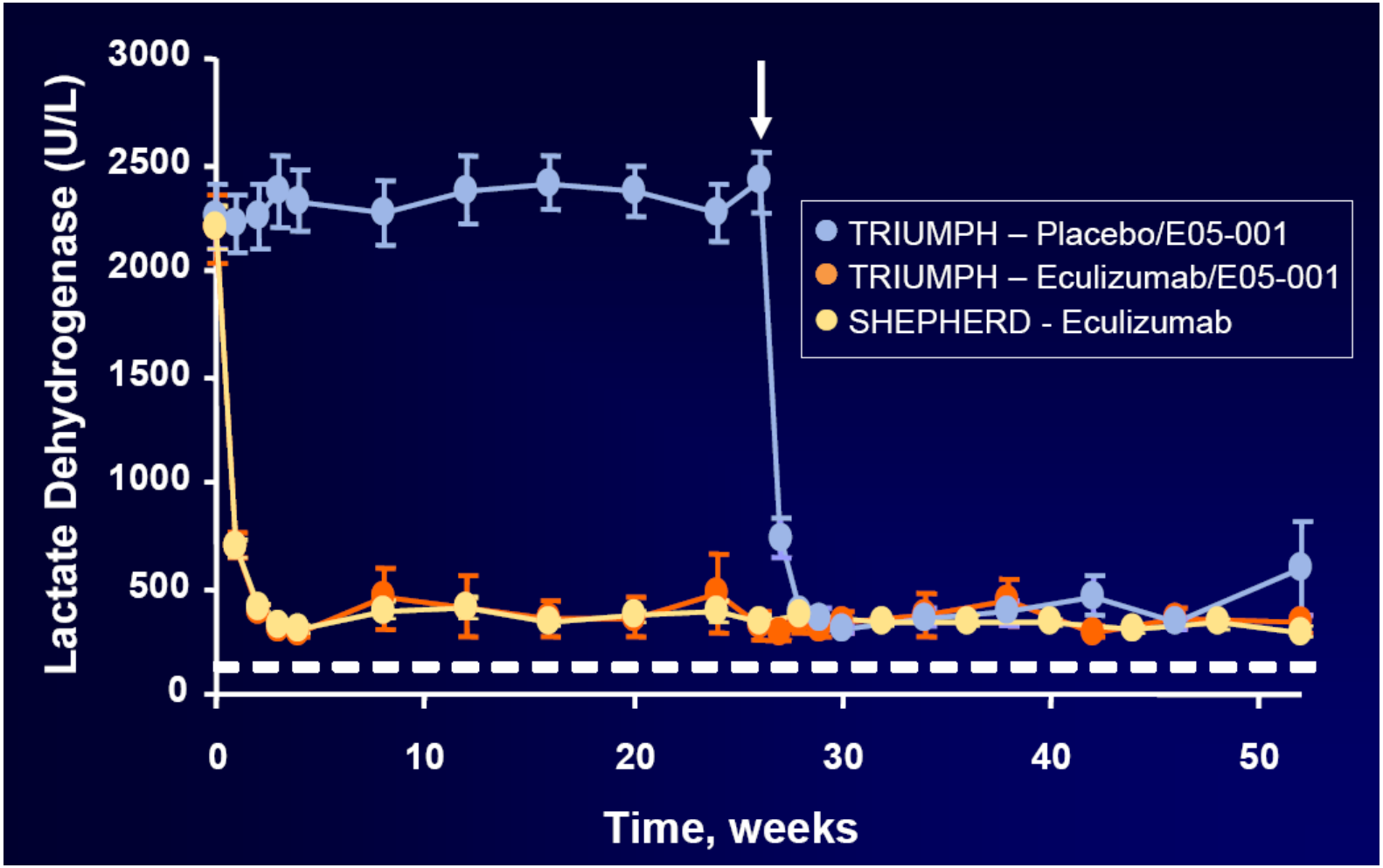
Anémie

Rother et al. *Nature Biotechnol*. 2007

Eculizumab « Soliris »' story

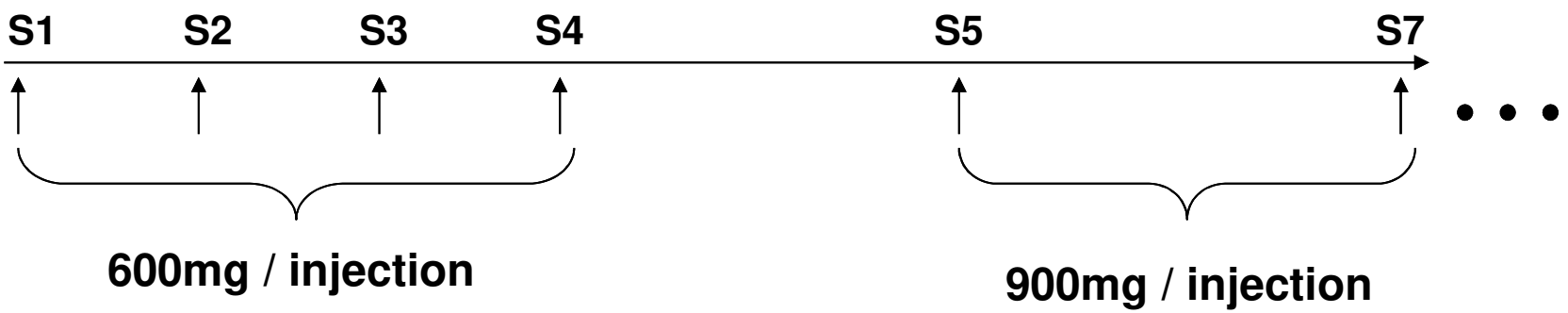


Efficacité immédiate sur l'hémolyse intra-vasculaire (HPN)



Hillmen P et al. NEJM 2006

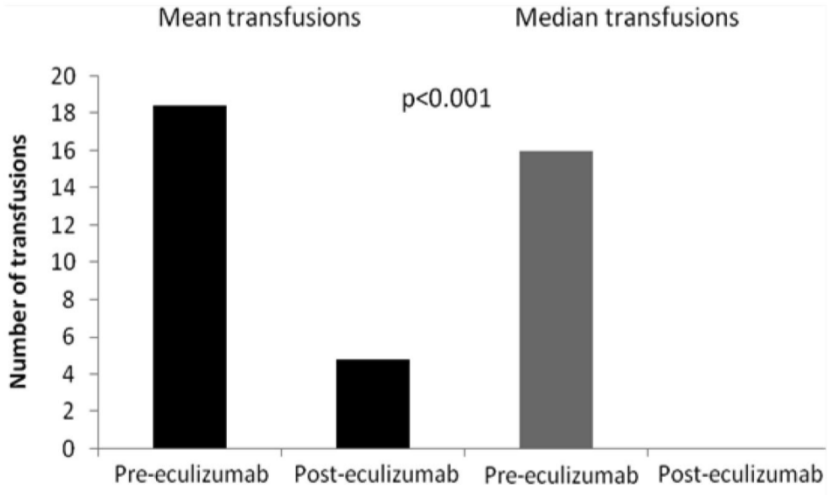
AMM dans l'HPN depuis Juin 2007



Recommandations européennes d'utilisation : http://www.ema.europa.eu/docs/fr_FR/document_library/EPAR_-_Product_Information/human/000791/WC500054208.pdf

Efficacité à long terme dans l'HPN

Sur l'anémie hémolytique:



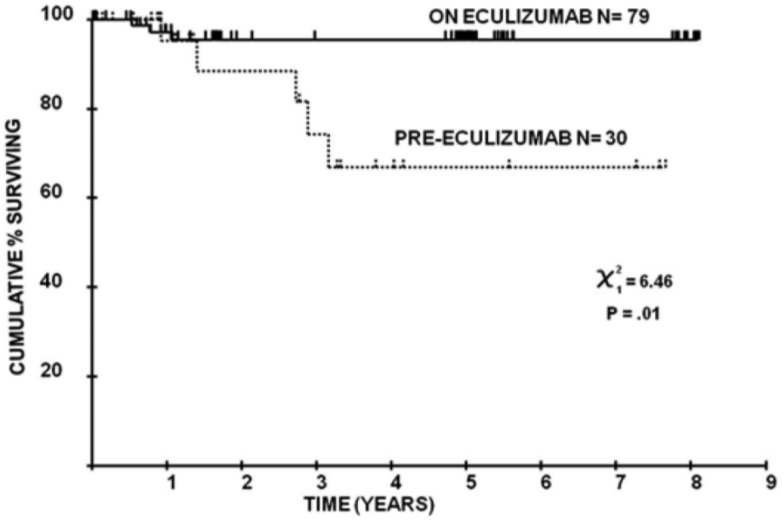
Besoin transfusionnel des 12 mois avant mise sous traitement et les 12 derniers mois sous eculizumab chez
64 patients.

Kelly, Blood, 23, 2011

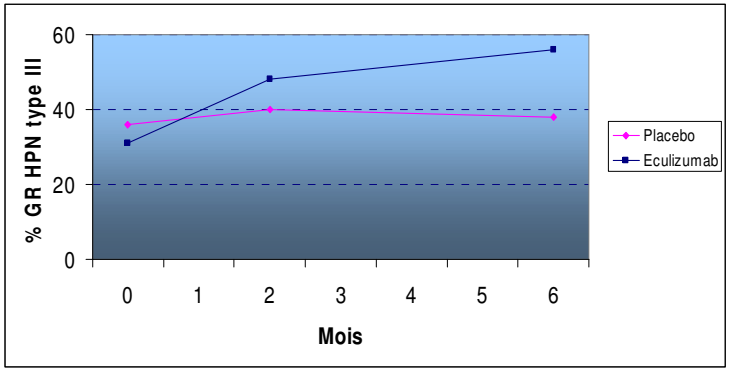
Sur les évènements thrombotiques:

Avant anti-C5 : 5.5 evts/100 an-patients
Sous anti-C5 : 0.8 evts/100 an-patients
p<0.001

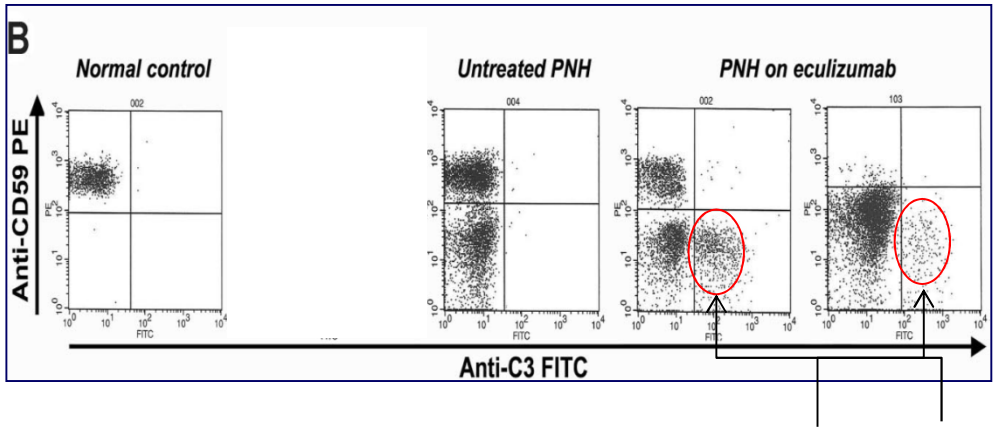
Sur la survie:



Oui, mais…



Augmentation du % PNH RBC :
Risque d'hémolyse aigue si arrêt du traitement :compliance++

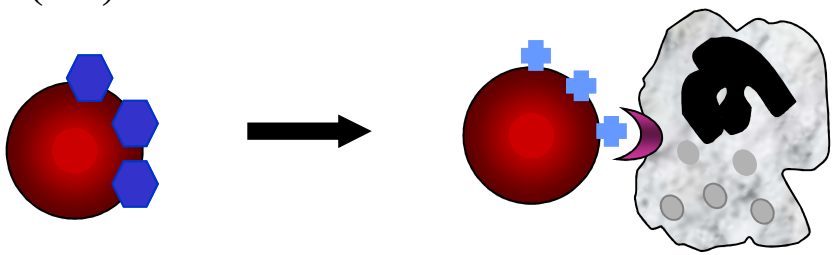


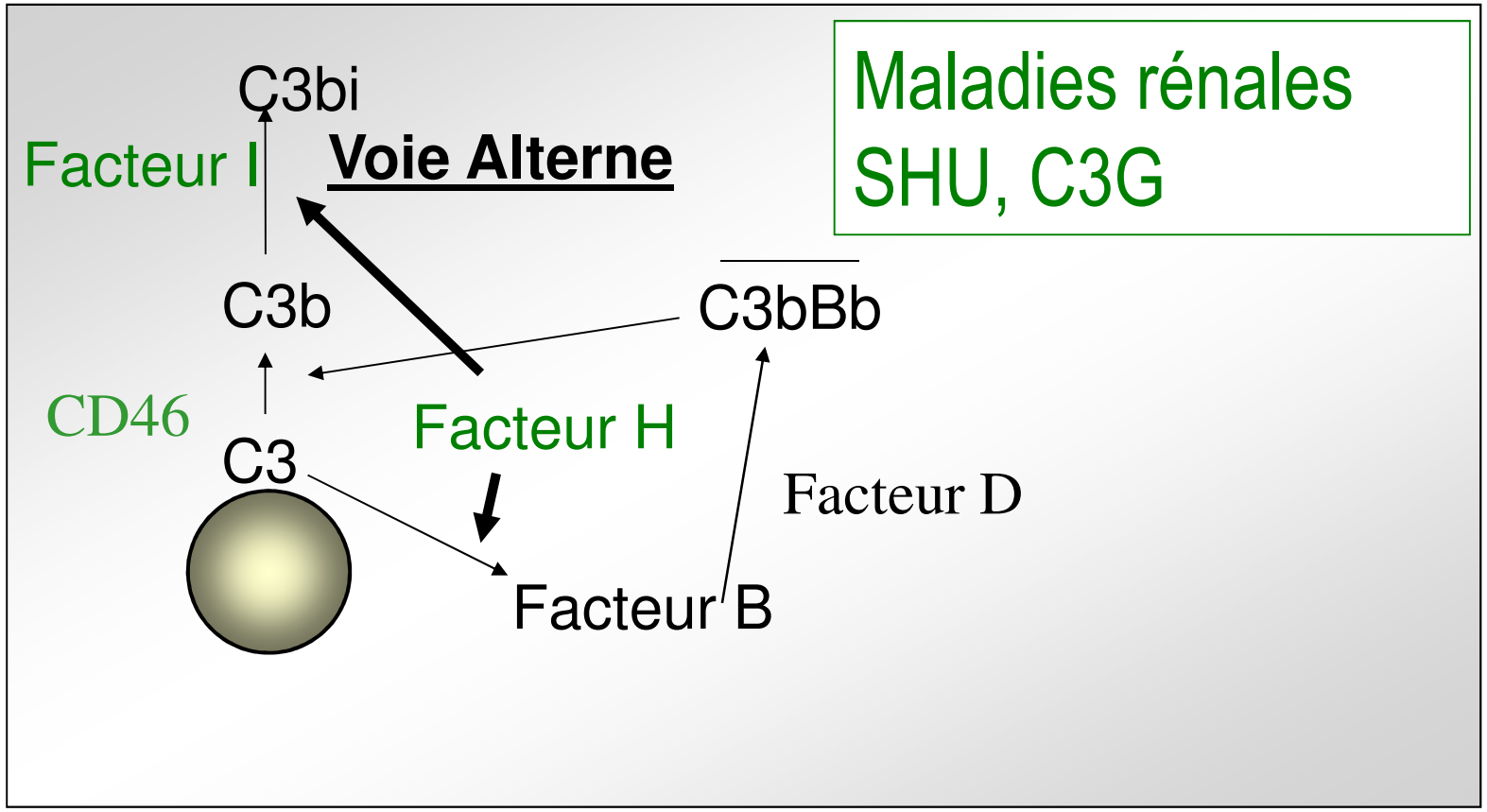
30% avec une hémolyse persistante

Evidence for C3 Opsonization of RBC : extravascular hemolysis?

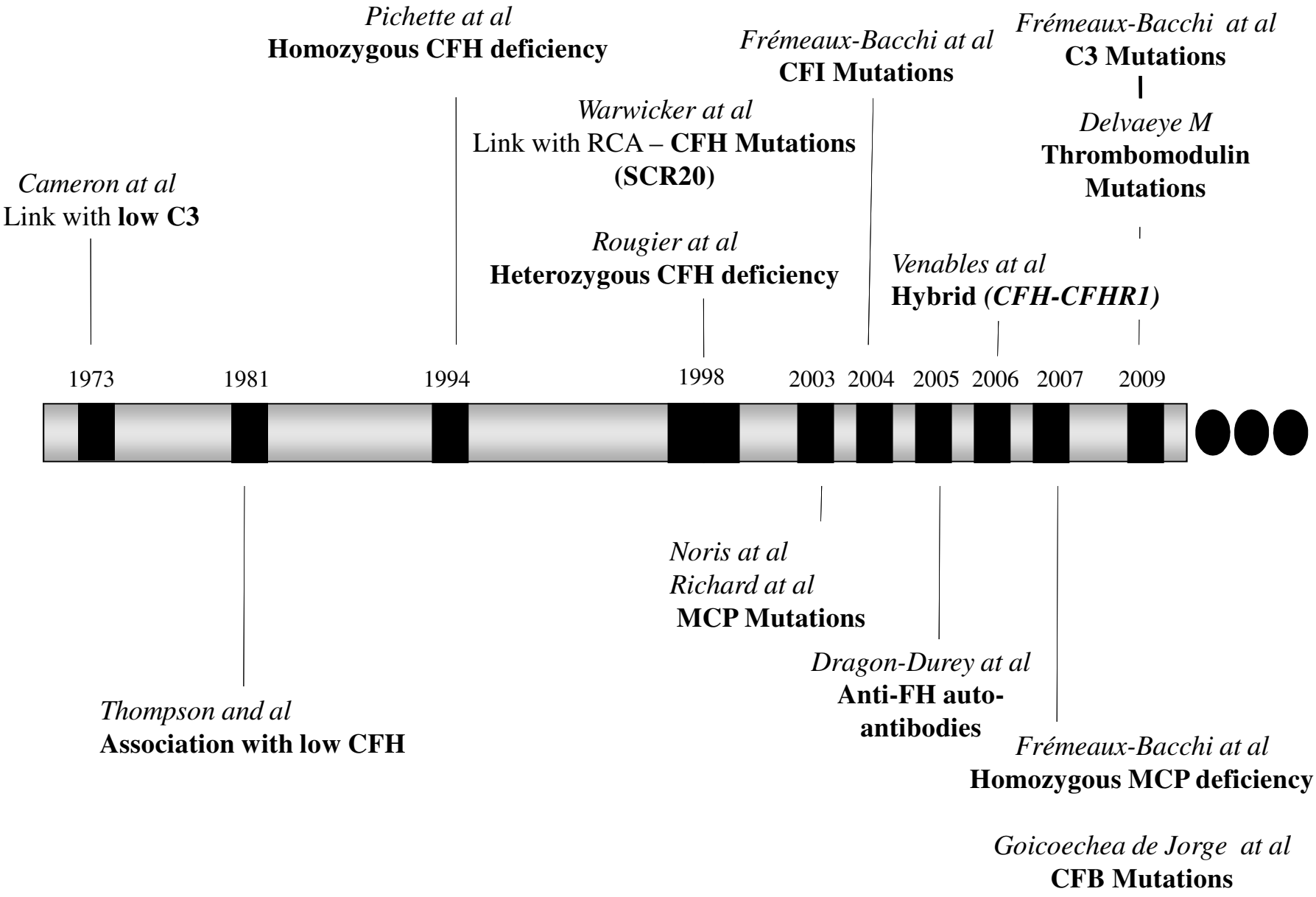
Risitano A et al. Blood 2009

Opsonisation (C3)




Maladies rénales
SHU, C3G
C3bi
Facteur I
Voie Alterne
C3b
C3bBb
CD46
Facteur H
C3
Facteur D
Facteur B

The aHUS' story



Etiologies du SHUa

- **1/ Déficits quantitatifs et mutations « perte de fonction »:**

  Gènes des protéines de régulation de la voie alterne du Complément :
  Facteur H, Facteur I, CD46 (Membrane Cofactor Protein)

- **2/ Mutations « gain de fonction » :**

  Gènes des composants de la C3 convertase alterne : Facteur B, C3

- **3/ Implication de polymorphismes génétiques**

  Polymorphismes dans le RCA : FH, CD46, nombre d'allèles CFHR

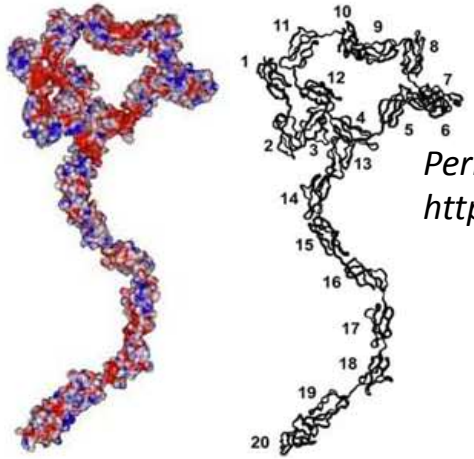
- **4/ A part ?** :

  formes acquises :

  - auto-anticorps anti-facteur H et SHUa

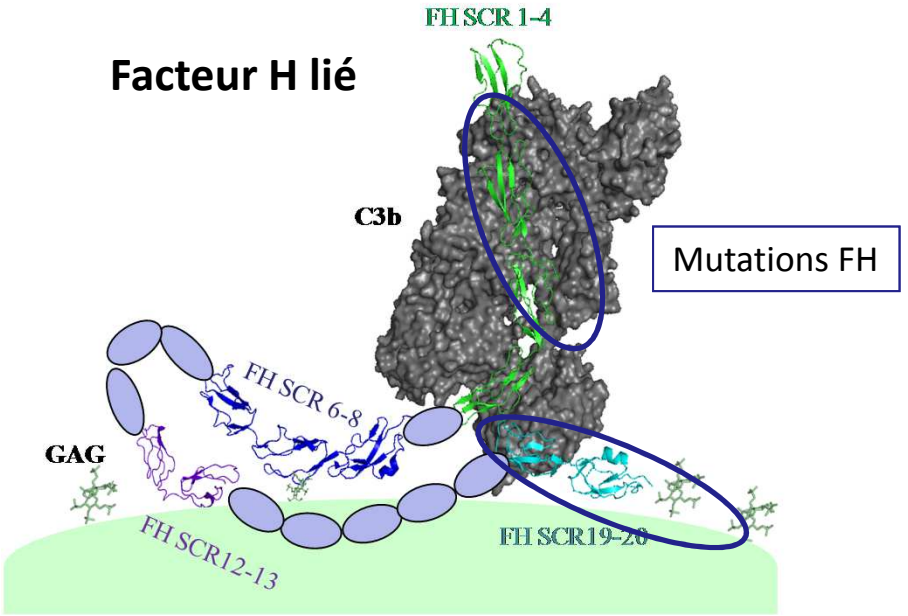
Complement Facteur H: Le gène le plus fréquemment impliqué dans les formes génétiques

Factor H en phase fluide

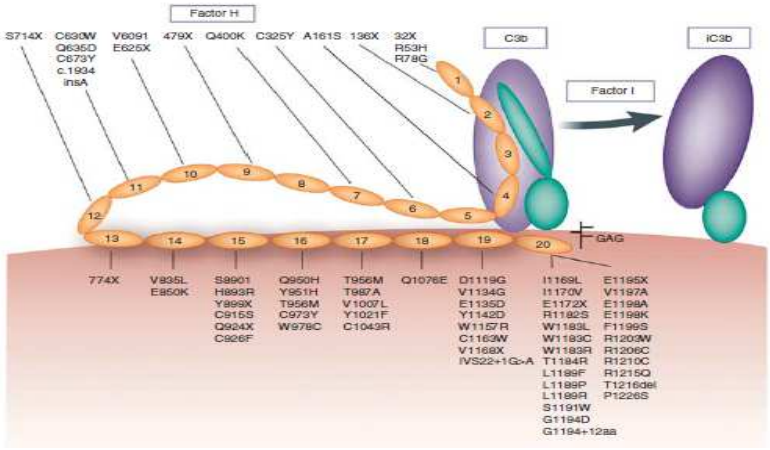


Perkins, https://www.ucl.ac.uk

Facteur H lié



L Roumenina , adapted from Morgan, Nat Struct Mol Biol, 2011



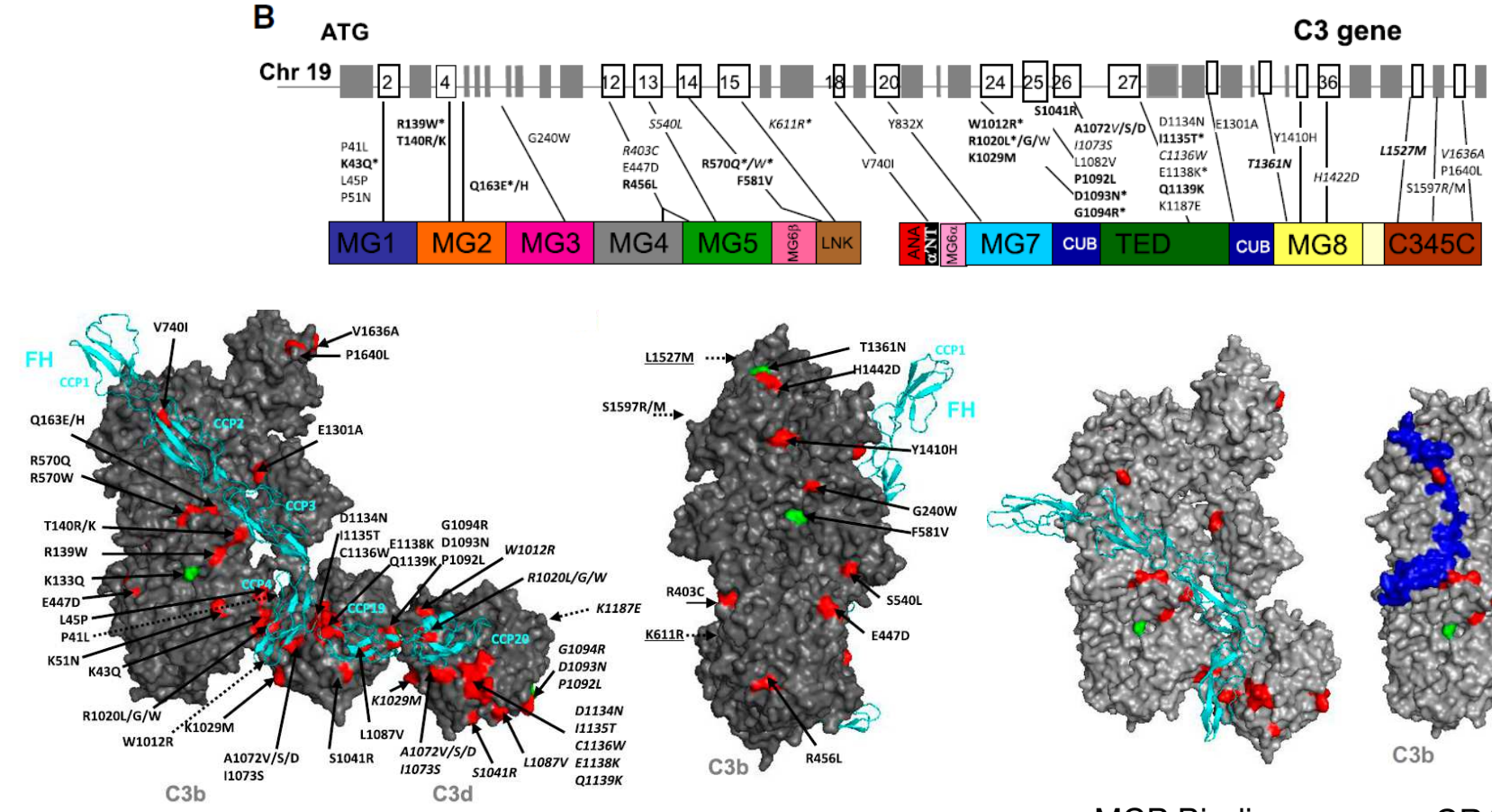
Kavanagh, Kidney Int , 2012

Mutations dans 25-30% des cas sporadiques
40% des cas familiaux
>150 mutations identifiées

Conséquences des mutations :
-déficits quantitatif
- mutations « perte de fonction »

C3 mutations

Found in 2-8% of aHUS patients,
Frequently associated with low C3 plasma levels



Schramm, Blood, 2015 FH Binding

The functional consequences of the C3 mutations vary according to their location but majoritarily the C3 mutated protein escapes the regulation

1ère observation de SHUa résistant aux échanges plasmatiques traité par l'eculizumab *Gruppo, NEJM 2009*

Garçon de 18 mois, (pas de mutation)

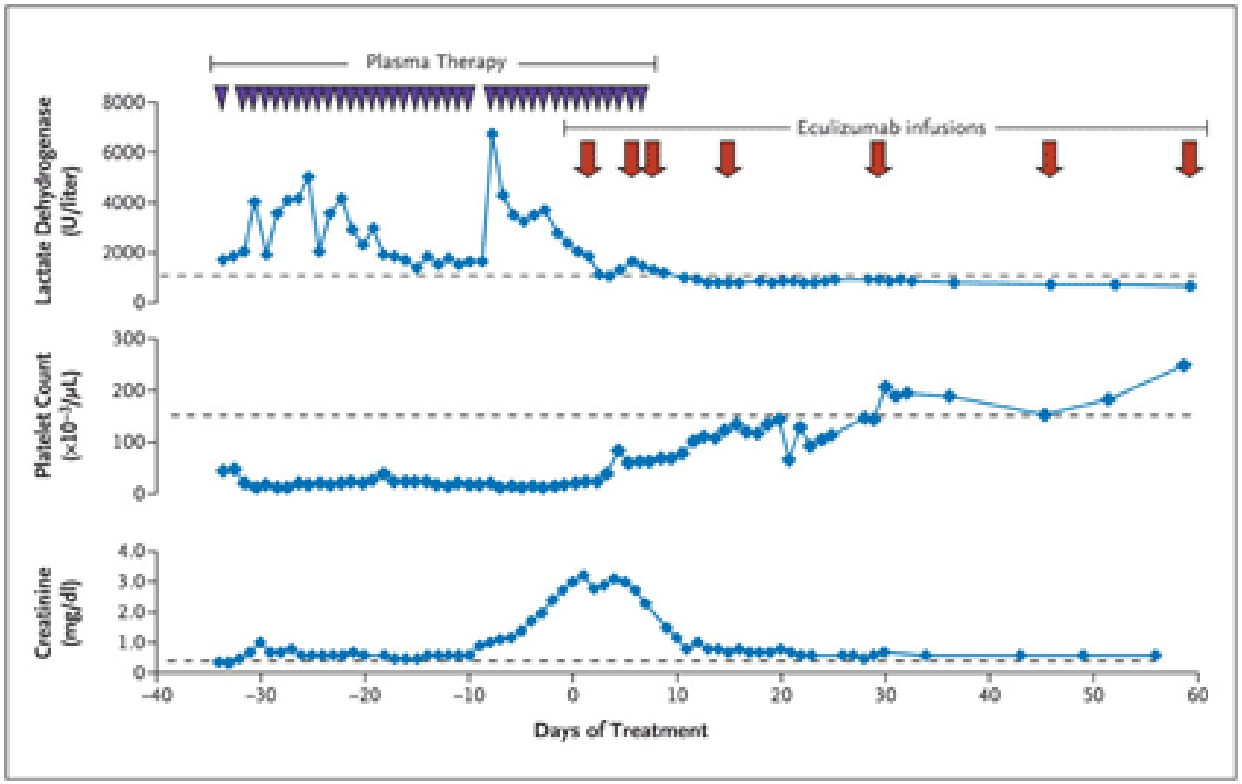
SHU à l'âge de 8 jours, rechutes à 3, 9 et 11 mois , plasma sensibles

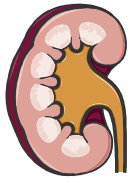
4eme rechute 2 mois après l'arrêt du PFC

Résistance à 32 échanges plasmatiques (quotidiens)

→ eculizumab 600 mg → rémission en 10 jours

rémission persistante sous 600 mg toutes les 2 semaines, recul 4 mois





Eculizumab Soliris® and aHUS

- **New avenue for aHUS treatment**
  - 25 patients treated in off-label studies
  - 15 were presented: 7 children / 8 adults
  - 9 and 6 involved native and transplanted kidneys, respectively
  - *CFH* (n=4), *C3* (n=1), no mutation identified (n=10)
  - **HUS remission was achieved in 100% of cases**
  - 8/15 (53%) still under treatment

Gruppo 2009; Nurnberger 2009; Chatelet 2009; Davin 2009; Legault 2009; Fremont 2009; Mache 2009; Haffner 2010; Lapeyraque 2010; Tsahumi 2010; Larrea 2010; Zimmerhackl 2010; Ardissimo 2010; Loos 2010

- **Four clinical trials of eculizumab in HUS patients**
  - the 4 studies have achieved the Company's enrollment targets

Eculizumab clinical trials in aHUS

Name	Age	Open	Stop	Criteria	patients
Adults PlasmaR aHUS	>18	May 2009 (26 w)	Dec2012	Low Pt desp 4WPT LDH ↗ Creat ↗ No Hemodialysis	15
Adults PlasmaS aHUS	>18	May 2009 (26 w)	Dec2012	↗ 25% Pt/// avt ttt LDH ↗ Creat ↗ No Hemodialysis	15
Adolescents PlasmaR aHUS	12-18	May 2009 (26 w)	Dec2012	Low Pt desp 4WPT LDH ↗ Creat ↗ No Hemodialysis	15
Adolescents PlasmaS aHUS	12-18	May 2009 (26 w)	Dec2012	↗ 25% Pt/// avt ttt LDH ↗ Creat ↗ No Hemodialysis	15

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

http://www.clinicaltrials.gov/ct2/results?term=eculizumab&pg=1

Autorisation pour le traitement du SHUa : FDA : 23 Sept 2011
CEE : 30 Nov 2011

The NEW ENGLAND JOURNAL of MEDICINE

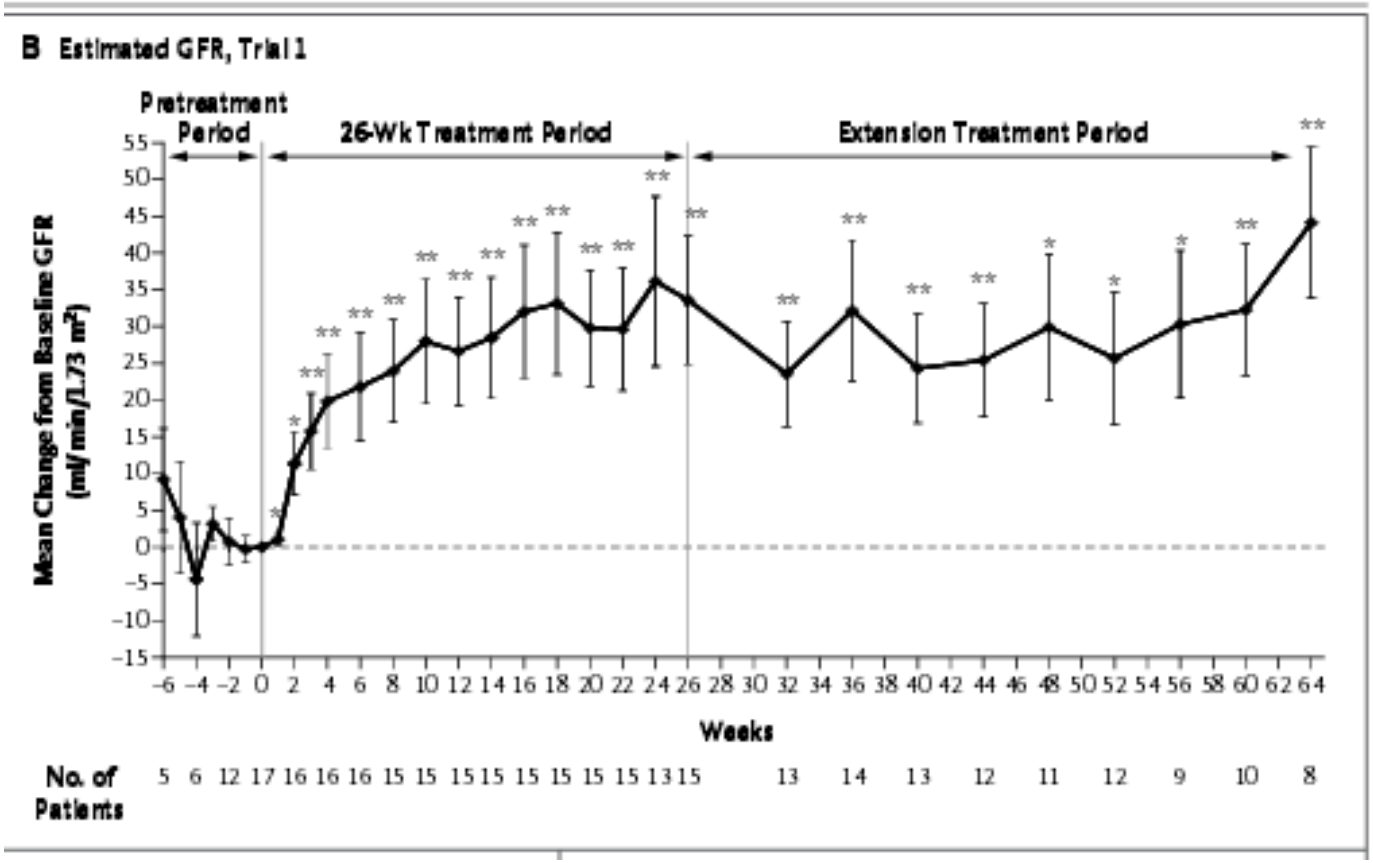
N Engl J Med 2013;368:2169-81

ORIGINAL ARTICLE

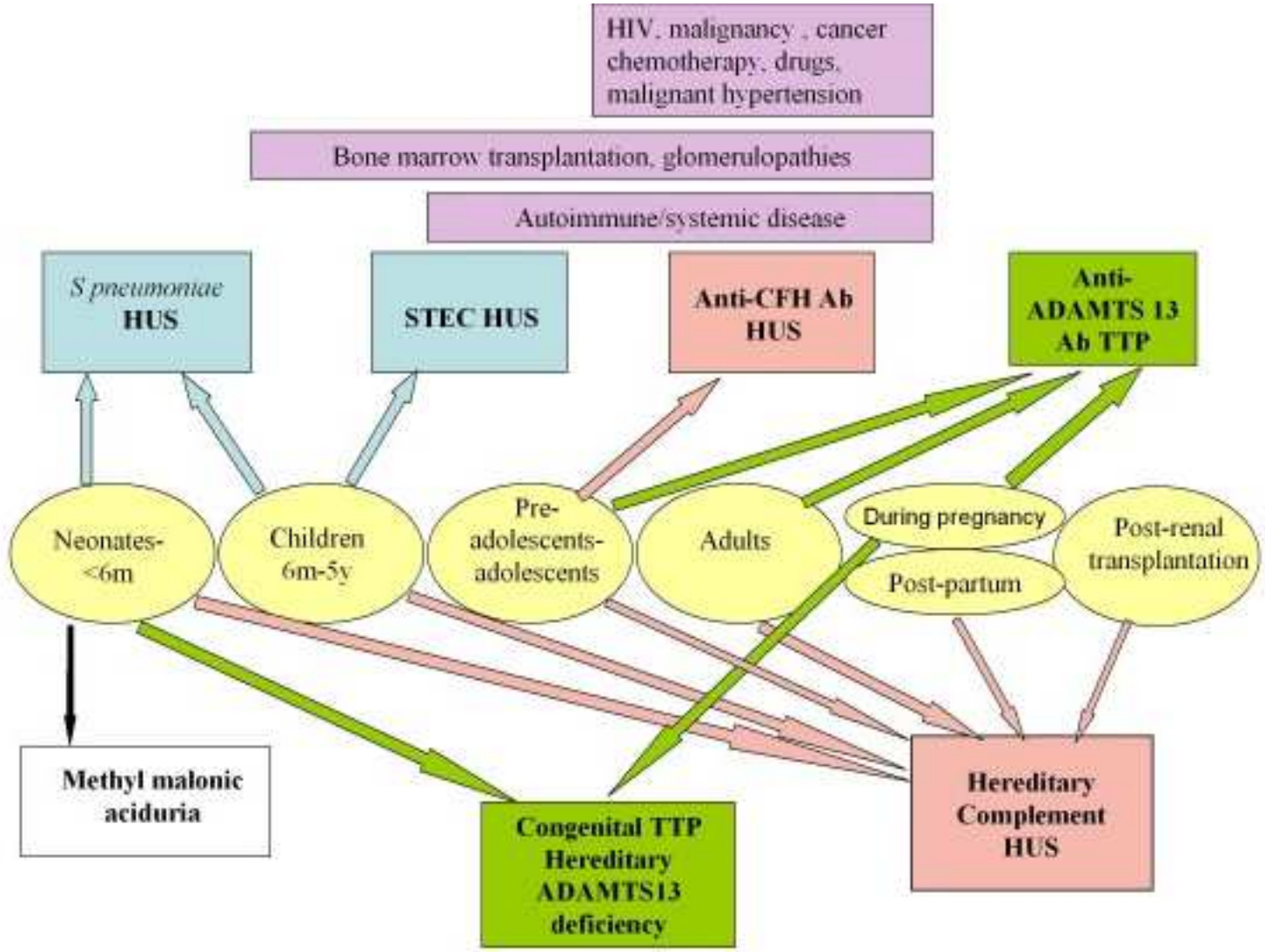
Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl, * T. Goodship, and C. Loirat

2 études prospectives (plasma-résistants, plasma dépendants)
37 patients



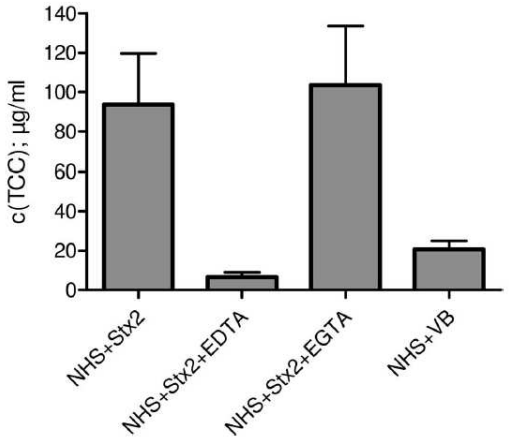
HUS aetiologies

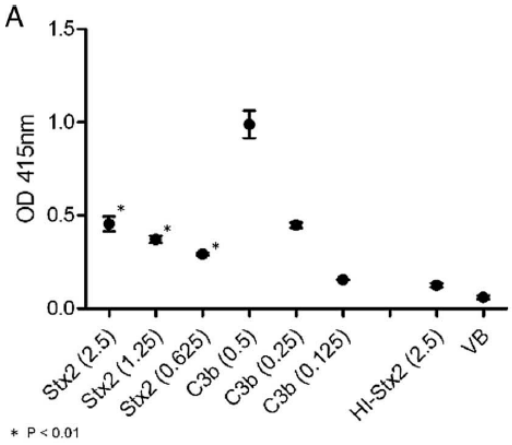


Fremeaux-Bacchi, Loirat , Orphanet J Rare Dis. 2011

HUS post -STEC

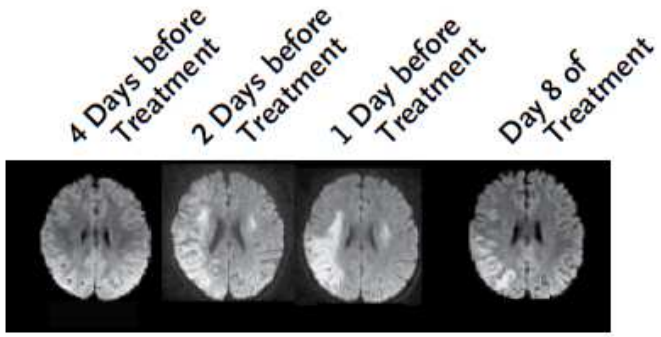
Link between STx-HUS and Complement ?



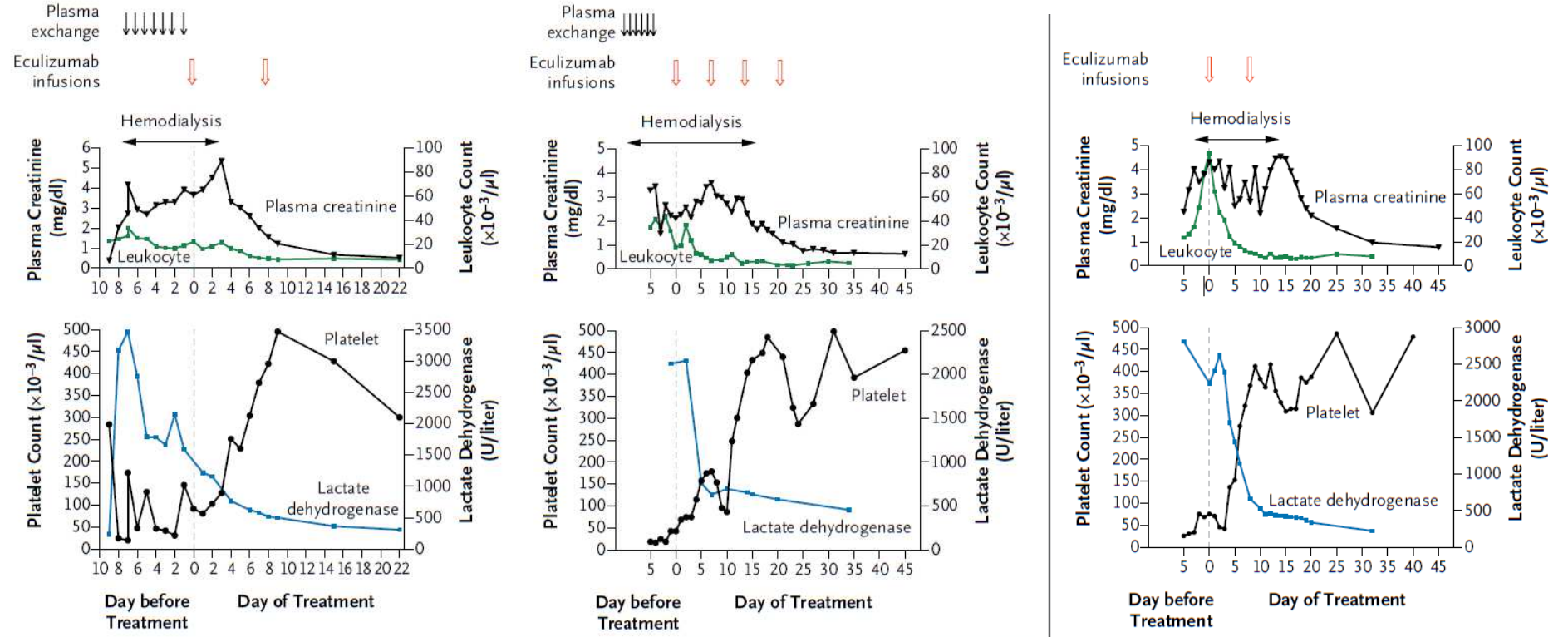


Orth, J Immunol, 2009

Eculizumab in Severe Shigatoxin–Associated HUS

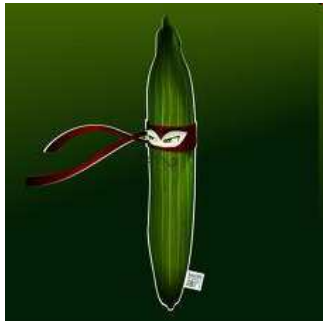


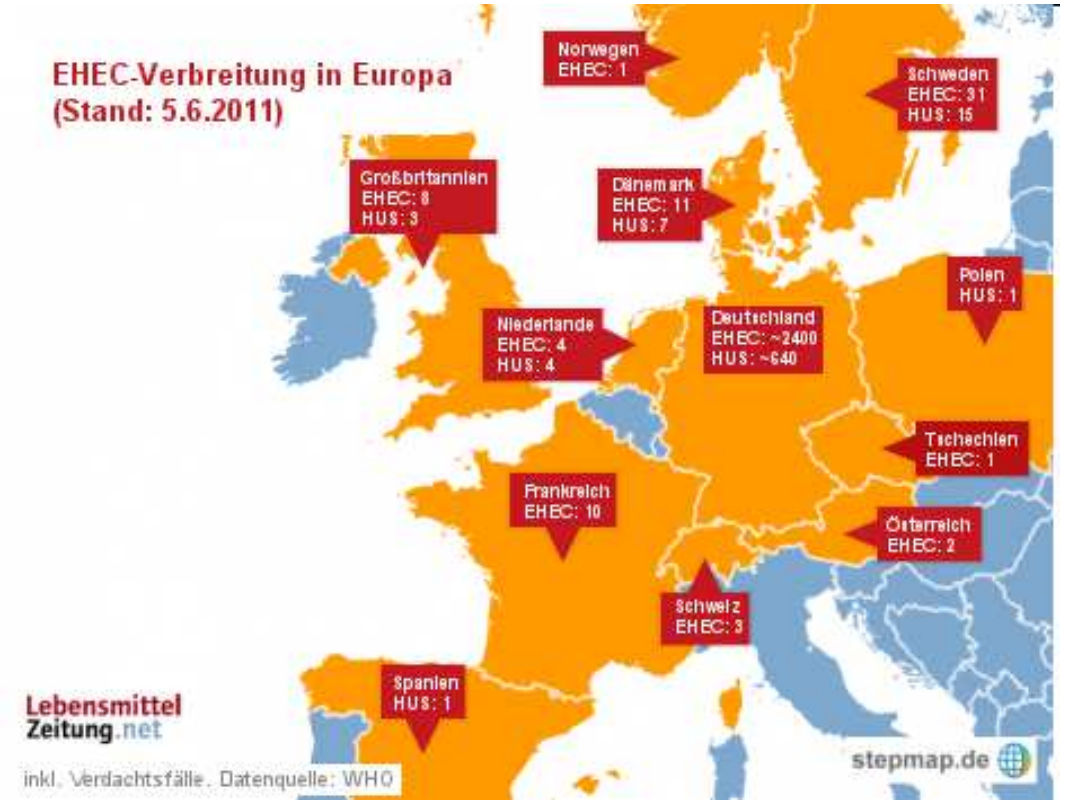
Sellier, NEJM, 364;26 nejm.org june 30, 2011



Patient 1 **Patient 2** **Patient 3**

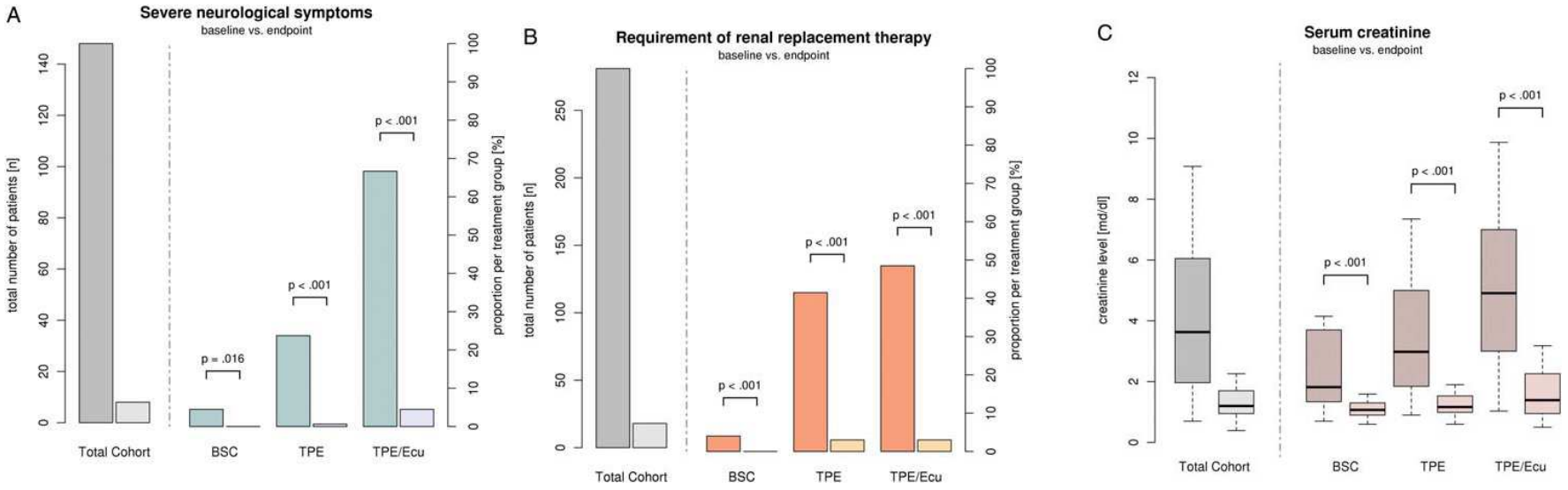
German O104H4 E Coli outbreak

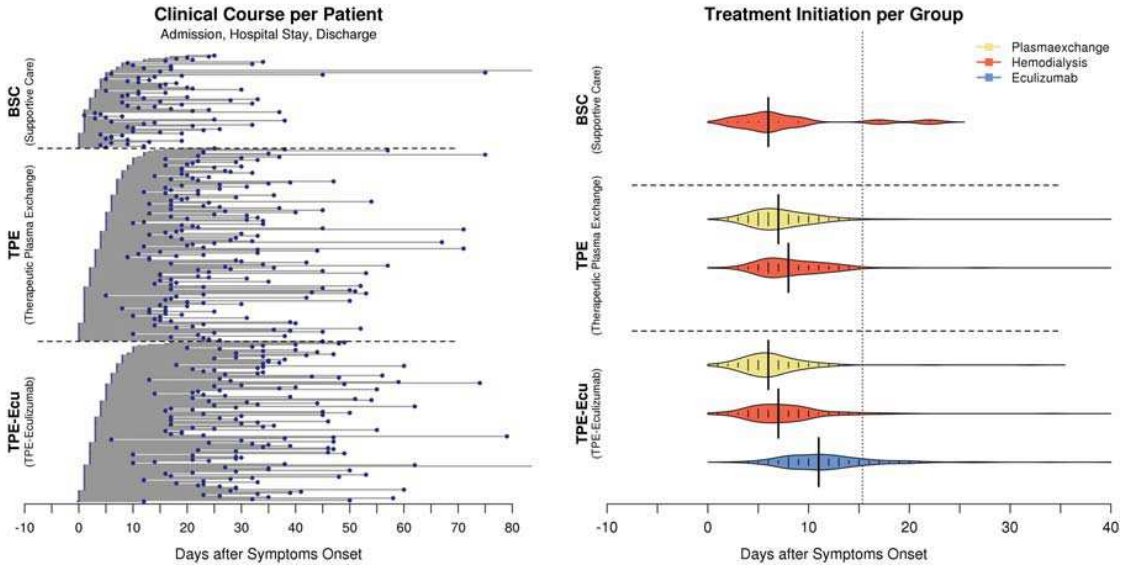




4321 outbreak cases : 3469 cases of Shigatoxin–producing *E. coli* and 852 cases of HUS, had been reported by July 26, 2011, when the outbreak was declared to be over.
50 Deaths

Comparison of treatments efficiency during the O104:H4 outbreak





Kielstein, J T, NDT, 2012

Further HUS Trials

Name	Age	Open	Stop	Criteria	patients
Adults aHUS (Doses 600, 900, 1200 mg)	>18	Jul2010 (26 w)	Sept2011	Low Pt LDH Creat No Hemodialysis	41
Pediatric aHUS (Fixed dosing based on weight)	1m-18Y	Sept 2010 (26 w)	July2012	Low Pt LDH Creat No Hemodialysis No PE>5 w	15
O104:H4 HUS in Begles	>2 Y	July 2011 (26 w)	Dec2012	Low Pt desp 4WPT LDH Creat No Hemodialysis	

Table 1. Characteristics of the patients in the order of HUS diagnosis

Patient #	Age, years	Sex	Contamination	Lowest platelet count, 1000/mm^3	Lowest Hb level, g/dL	Highest LDH IU/L ULN: 248 IU/L	Highest creatinine, µmol/L	Neuro	Heart troponin (× *N*)	Liver transaminases (×*N*)	Pancreas lipase (×*N*)	Other
W1	41	Female	Collective	14	6.6	2451	HD		67	3		
W2	64	Female	Collective	14	6.8	2568	HD	a	23	2	4	Lung
W3	49	Female	Collective	23	5.0	1520	150			10	7	
W4	31	Female	Collective	26	6.1	1981	366	b	8	2	3	
M1	34	Male	Collective	24	6.3	1611	255	c		4		Skin
W5	46	Female	Collective	92	6.2	613	68			12		
M2	41	Male	Collective	86	10.7	607	152			2		
W6	4	Female	Household	93	9.7	533	48			2		
W7	36	Female	Household	86	8.5	510	69			1.5		

Enzyme serum levels are presented as × times the upper limit of normal (ULN).
Neurological signs: a: encephalitis, coma, seizures; b: psychiatric, binocular diplopia, pyramidal syndrome; c: static and kinetic cerebellar syndrome.
Hb, haemoglobin; HD, haemodialysis.

NDT Advance Access published November 28, 2013

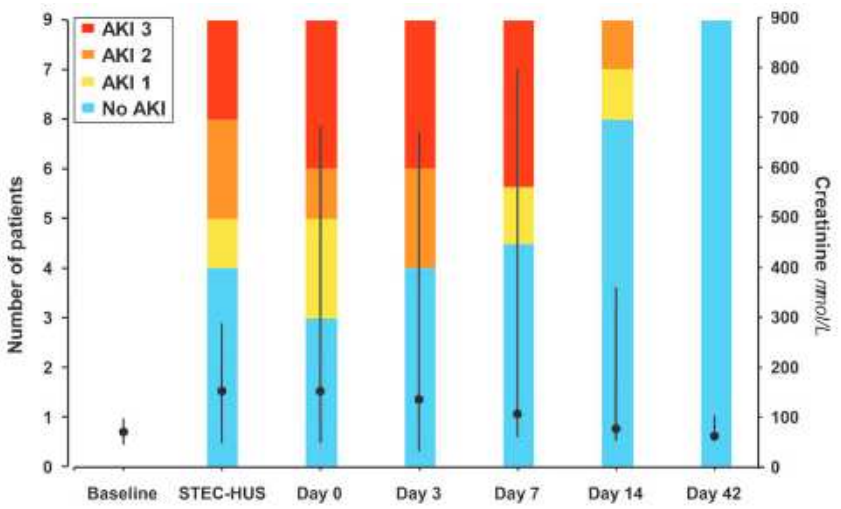
Nephrol Dial Transplant (2013) 0: 1–9
doi: 10.1093/ndt/gft470

ndt Nephrology Dialysis Transplantation

Original Article

Outbreak of *Escherichia coli* O104:H4 haemolytic uraemic syndrome in France: outcome with eculizumab

Yahsou Delmas[1], [1]Service de Néphrologie Transplantation Dialyse, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France.



PATIENTS WITH AHUS ON RENAL OUTCOMES: A POOLED ANALYSIS

John Kincaid, Crit Care Med. 2015 Dec;43(12 Suppl 1):244

Learning Objectives: Comparison of the effect of Eculizumab on renal function in Atypical hemolytic uremic syndrome patients starting treatment ≤7 d with those starting >7 d after the currentTMA manifestation.

Methods: Data from pediatric and adult pts with aHUS with documented date of onset of current TMA manifestation and baseline (BL) estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m2 from 4 phase 2, open-label, single-arm trials of ECU were pooled.

Results:

Median age at enrollment : 29 (0–80) y

Duration of current manifestation to start of ECU: 23 (1-1447) d.

Time between onset and TTT initiation	Eculizumab < 7j	Eculizumab >7j
Nb Patients	21	76
Median Baseline eGFR (mL/min/1,73 m2)	11	16
Mean change at 6 Mo	57	23
Mean change at 1 Y	57	21

BL characteristics that independently contributed to eGFR improvements at 6 mo :

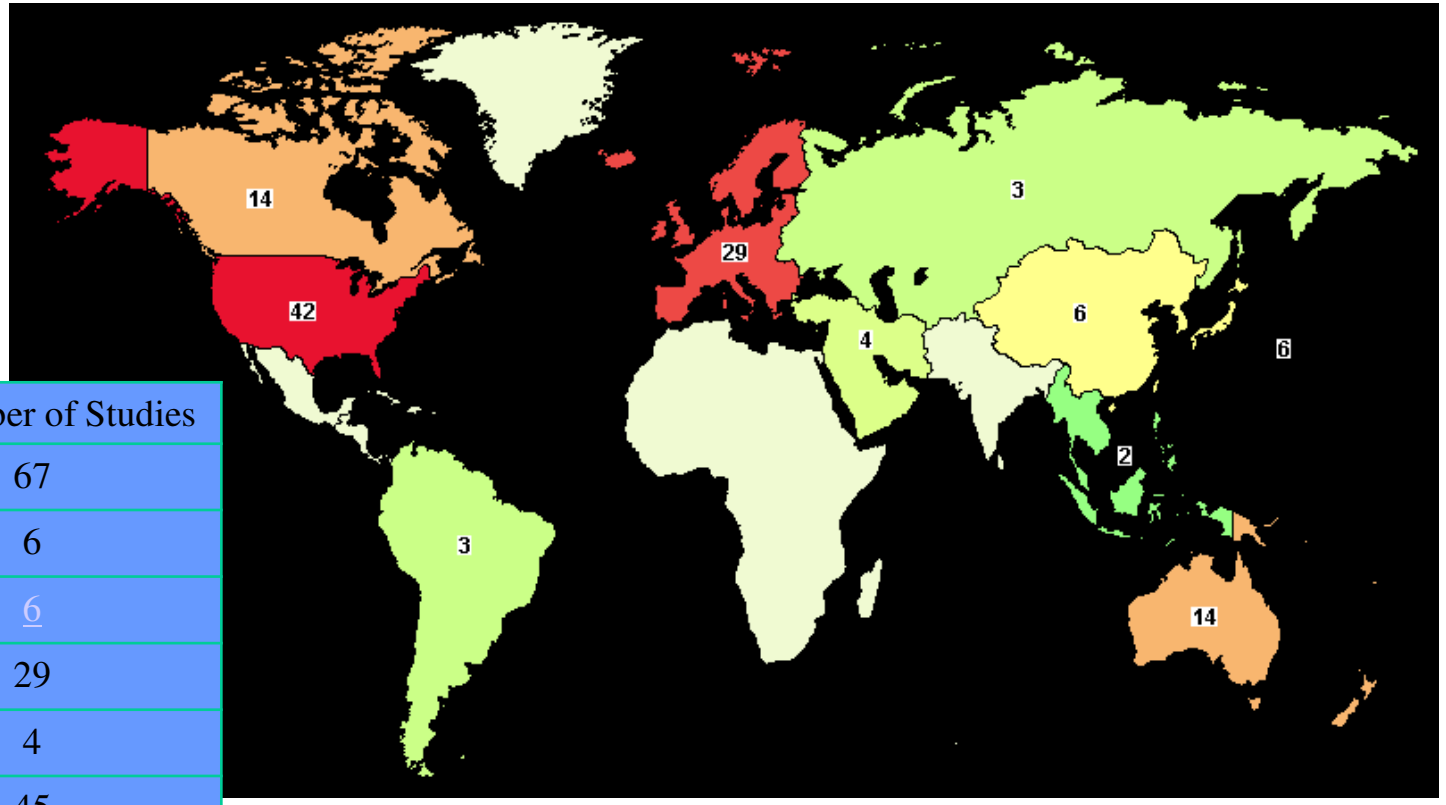
age (coefficient, -0.81; P<0.0001),

LDH level (0.09; P=0.005),

duration of current TMA manifestation prior to eculizumab (-0.22; P=0.005),

single vs multipleTMA manifestation history (P=0.01).

Other On going trials…(Altogether n=67)



Region Name	Number of Studies
World	67
East Asia	6
Japan	6
Europe	29
Middle East	4
North America	45
Canada	14
United States	42
North Asia	3
Pacifica	14
South America	3
Southeast Asia	2

Maladies auto-immunes, rejet de greffe, névrite optique….

A year's treatment costs more than US$400,000…

IMMUNOBIOLOGY

BLOOD, 3 JANUARY 2013, VOLUME 121,

CD59 deficiency is associated with chronic hemolysis and childhood relapsing immune-mediated polyneuropathy

*Yoram Nevo,[1] *Bruria Ben-Zeev,[2] Adi Tabib,[3] Rachel Straussberg,[4] Yair Anikster,[5] Zamir Shorer,[6] Aviva Fattal-Valevski,[7] Asaf Ta-Shma,[8] Sharon Aharoni,[4] Malcolm Rabie,[1] Shamir Zenvirt,[8] Hanoch Goldshmidt,[9] Yakov Fellig,[9] Avraham Shaag,[8] †Dror Mevorach,[3] and †Orly Elpeleg[8]

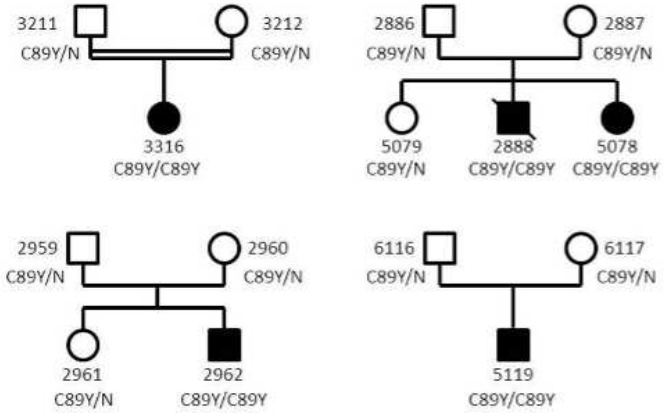
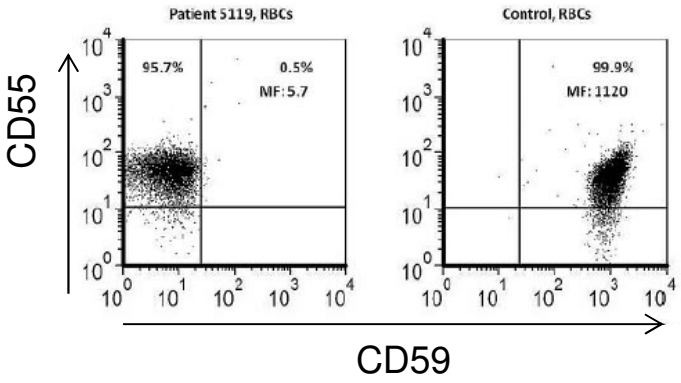
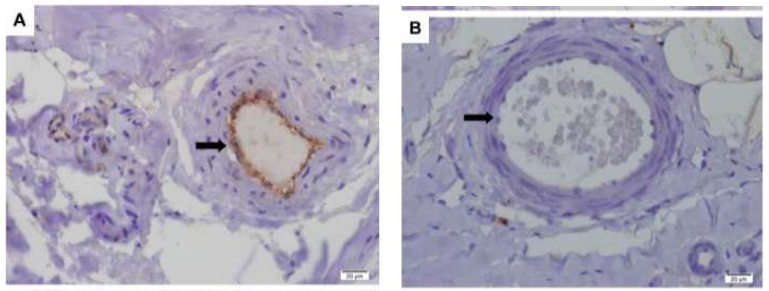


Figure 1. Pedigree of the families of identified patients.

Sd de Guillain-Barré récurrent précoce
Anémie (Hb 6-12g/dL)
Hémolytique (LDH>2 à 4x N, hapto<N/10)
Plaquettes normales

Démyélinisation des fibres motrices et sensorielles avec atteinte axonale





Défaut d'expression de CD59 sur les vaisseaux péri-axonaux.
Atrophie axonale

Réversibilité des lésions neuronales??

CORRESPONDENCE

Targeted Therapy with Eculizumab for Inherited CD59 Deficiency

N Engl J Med 2014; 370:90-92 | January 2, 2014 | DOI: 10.1056/NEJMc1308104

Table 1. Laboratory Results and Clinical Findings in the CD59-deficient Patient at Initial Diagnosis and during the Observation Period.*

Variable	Normal Range	Age			Age			
		7 mo	18 mo	22 mo	30 mo	36 mo	55 mo	60 mo
Eculizumab therapy					Initiation	6 mo	25 mo	30 mo
Hemoglobin (g/dl)	9.2–15.5	11.1	4.3	5.3	9.4	9.5	11.7	10.8
White-cell count ($\times 10^{-9}$/liter)	6.0–17.0	8.1	5.9	16.8	5.5	7.0	12.8	7.0
Platelet count ($\times 10^{-9}$/liter)	200–360	591	76	482	427	481	509	433
Reticulocytes ($\times 10^{-9}$/liter)	22–76	Not performed	107	64	145	120	Not performed	174
Lactate dehydrogenase (U/liter)	164–286	342	3158	947	314	275	270	271
Bilirubin (mg/dl)	0.2–1.0	Not performed	1.2	0.5	0.6	1.2	0.6	Not performed
Aspartate aminotransferase (U/liter)	<50	38	148	55	27	24	37	34
C-reactive protein (mg/dl)	<0.5	0.3	1.4	2.0	2.4	<0.5	0.3	0.2
Haptoglobin (g/liter)	0.02–3.00	Not performed	<0.06	<0.06	<0.06	<0.06	<0.01	<0.01
Cerebral and spinal MRI		Cerebral MRI: normal; spinal MRI: contrast enhancement and thickening of dorsal-nerve roots at conus and cauda	T_2-weighted hyperintense lesions from right superior colliculus and adjacent central tegmental tract to superior cerebellar peduncles and downward to internal genu of the facial nerve and abducens nuclei; no restriction in diffusion and minimal gadolinium enhancement of right inferior colliculus; partial regression after 2 wk with only minor residuals in formerly contrast-enhancing inferior colliculus	Signs of minimal cortical edema with slight bilateral cortical diffusion restriction and similar findings in basal ganglia; regression of these findings after 2 wk; development of possibly glucocorticoid-induced cortical pseudoatrophy†; ongoing cortical pseudoatrophy shown on MRI several wk later	Not performed	Not performed	Almost complete normalization of cortical pseudoatrophy†; only minimal residuals at right inferior colliculus; complete regression of other brain-stem lesions	Not performed
MNCV and EEG studies		MNCV of peroneal and tibialis nerves not detectable	Not performed	EEG shows frontal spike-wave complexes on both sides	Not performed	MNCV of left tibialis nerve shows distal latency, 4.5 msec, velocity, 21 m/sec, amplitude, 0.19 mV	EEG shows slowing with some beta activity, without signs of convulsion	MNCV of left tibialis nerve shows distal latency, 3.5 msec, velocity, 29.5 m/sec, amplitude, 1.64 mV
Clinical neurologic findings		Bulbar symptoms: inability to swallow; generalized muscular hypotonia (legs flaccid and muscle reflexes absent)	Abducens and facial nerve palsy; progressive muscular hypotonia	Progressive neurologic impairment: focal seizures, bulbar symptoms, generalized muscular hypotonia, ventilation required	Ongoing bulbar symptoms, generalized muscular hypotonia, ventilation required	Ongoing bulbar symptoms, generalized muscular hypotonia, ventilation required	Ventilation and tracheostomy no longer required; movement of arms and legs against resistance; can sit and stand with assistance; speech poor; sufficient cognitive function	Normal swallowing and eating; speech improved (phrases with 3 or 4 words); can stand upright for a short time; cannot walk
Other findings		Cerebrospinal fluid analysis shows normal cell count with slightly elevated protein level (69.2 mg/dl)	Hemolytic crisis; acute kidney failure (renal histologic findings show thrombotic microangiopathy)	Fever; obstruction of respiratory tract with reanimation; retinal edema probably ischemic; hemolytic crisis (schistocytes, 0.9%)	Visual impairment	Visual impairment	Visual impairment	Visual impairment

* Direct antiglobulin tests were negative before and after the initiation of eculizumab. EEG denotes electroencephalography, MNCV motor nerve conduction velocity, and MRI magnetic resonance imaging.

† Pseudoatrophy is an apparent decrease in the volume of cortical tissue due to changes in production of cerebrospinal fluid and alterations in the blood–brain barrier.

NEJM, 2017

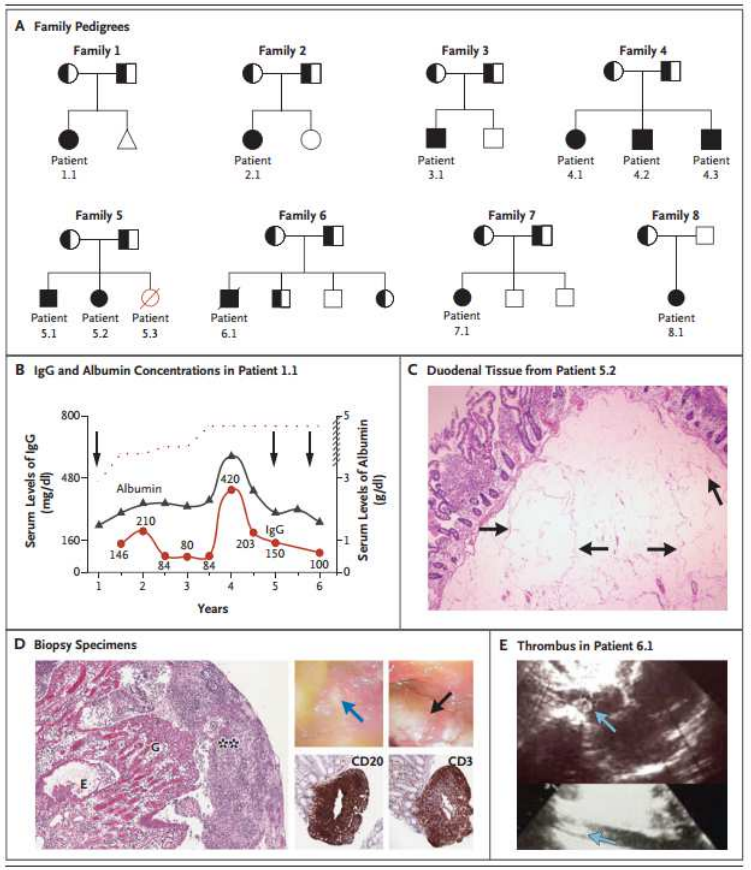
CD55 Deficiency, Early-Onset Protein-Losing Enteropathy, and Thrombosis

CHAPLE Syndrome

Table 1. Demographic and Clinical Characteristics of 11 Patients with the CHAPLE Syndrome.*

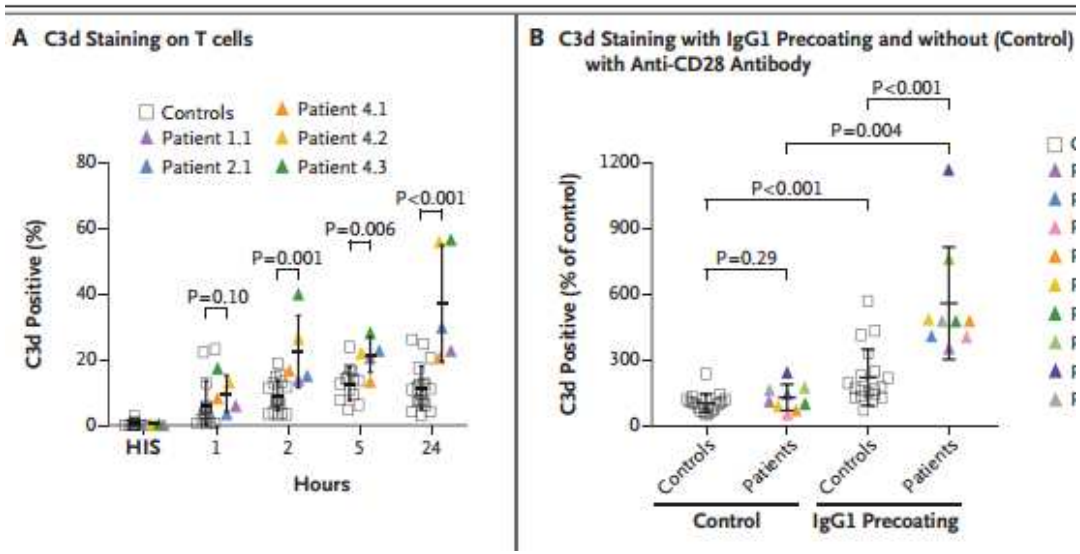
Characteristic	No. of Patients
Sex	
Female	6
Male	5
Age at presentation <2 yr	8
Manifestations of gastrointestinal disease or inflammatory bowel disease	
Chronic or recurrent diarrhea	8
Abdominal pain	4
Vomiting	6
Features of protein-losing enteropathy	
Hypoalbuminemia	10
Hypogammaglobulinemia	11
Facial or extremity edema	9
Confirmed primary intestinal lymphangiectasia or Waldmann's disease†	5
Malabsorption features	
Growth retardation	8
Anemia	9
Vitamin or micronutrient deficiency‡	11
Features of thrombotic disease§	
Thrombocytosis	2
Thrombosis	3
Endoscopic findings†	
Mucosal ulcer	4
Lymphoid infiltrates in mucosa	6
Recurrent lung infection	5
Additional features	
Hypothyroidism¶	3
Arthritis or arthralgia	2
Finger clubbing	5

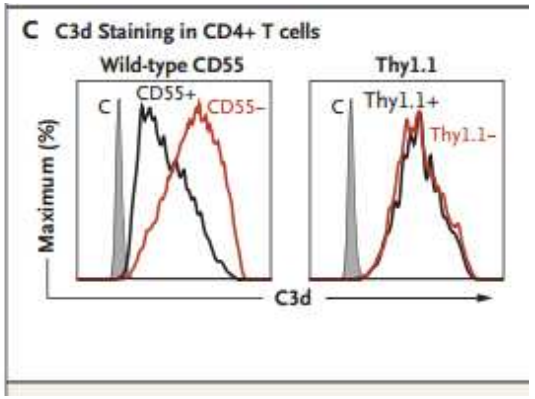
* The CHAPLE syndrome comprises CD55 (decay-accelerating factor) deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy.

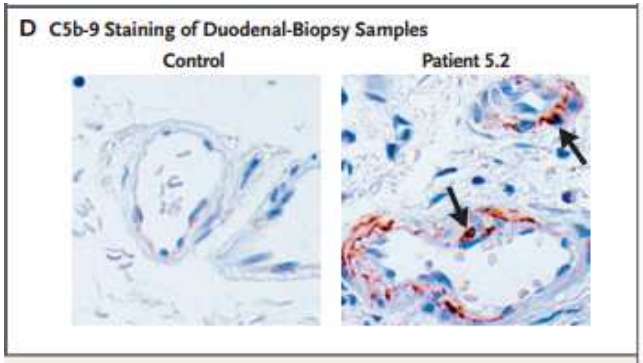


Elargissement des espaces lympho-vasculaires de la sous muqueuse
Infiltration par Granulocytes et des nodules lymphoïdes riches en LB et LT

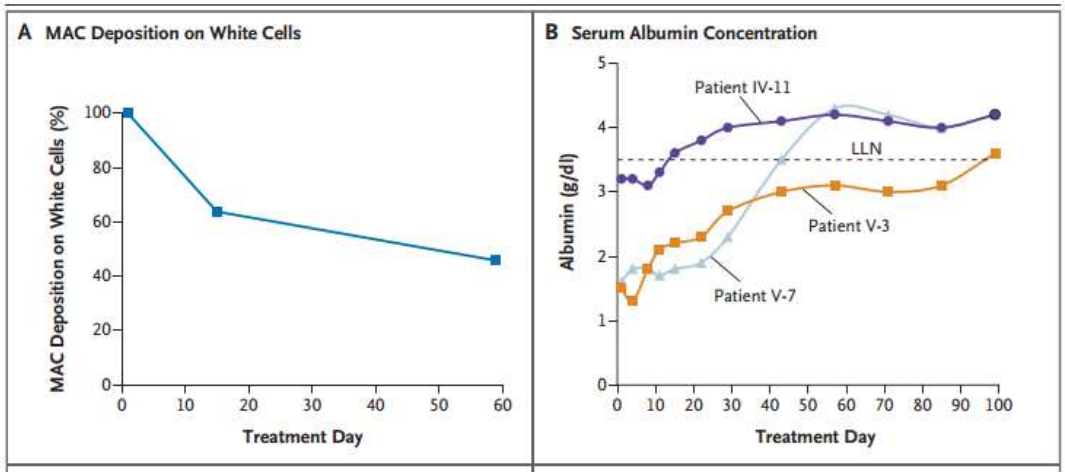
LT opsonisés et hyper-activés :

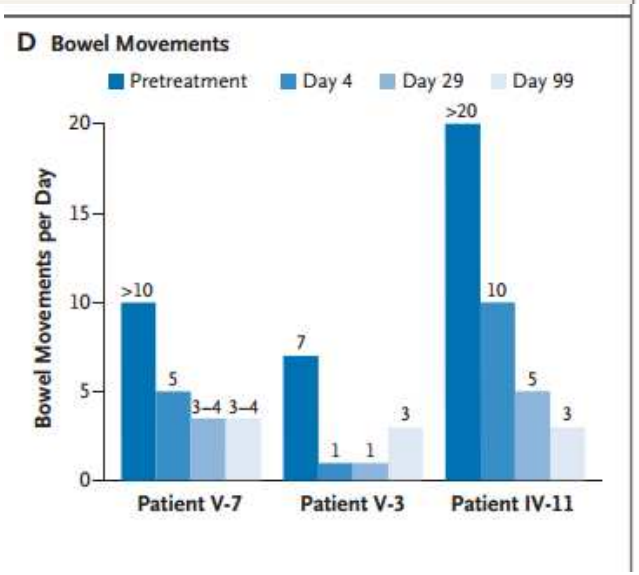




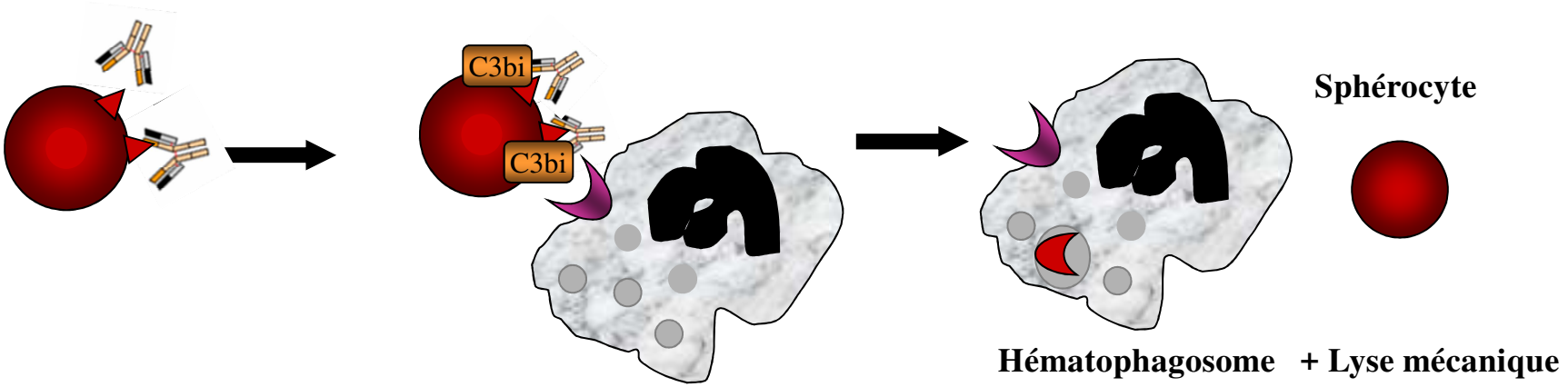


Evolution sous eculizumab :

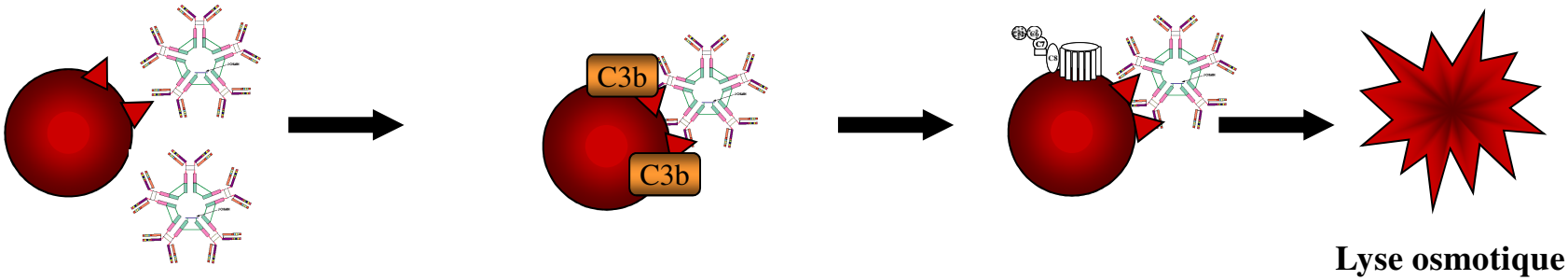




Rôle du complément dans les AHAI



Agglutinines "chaudes"

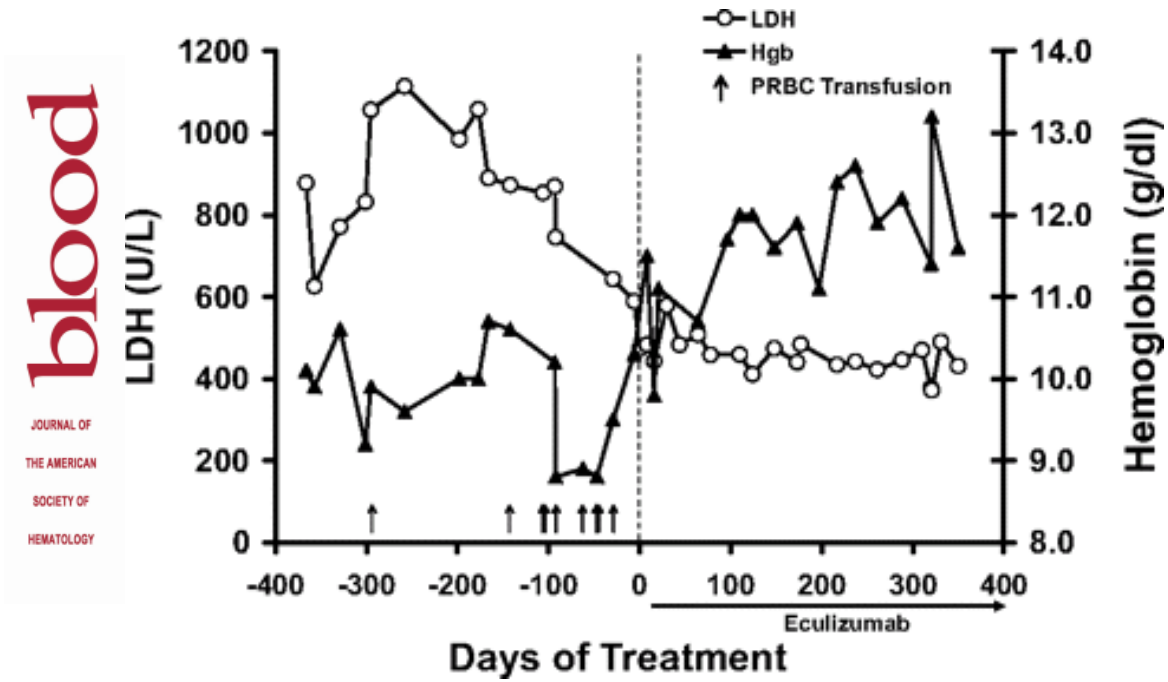


Agglutinines "froides"

Thérapeutique : Eculizumab

Anti-C5 (eculizumab, Soliris®) : Efficacité dans maladie à agglutinines froides

Long-term efficacy of the complement inhibitor eculizumab in cold agglutinin disease, Blood, 2009, Vol. 113, No. 16, pp. 3885-3886. A Röth, T Philipp



Essai Phase II DECADE

(02/2011, University Hospital, Essen, Fin Aout 2014)

Clinical Case Reports

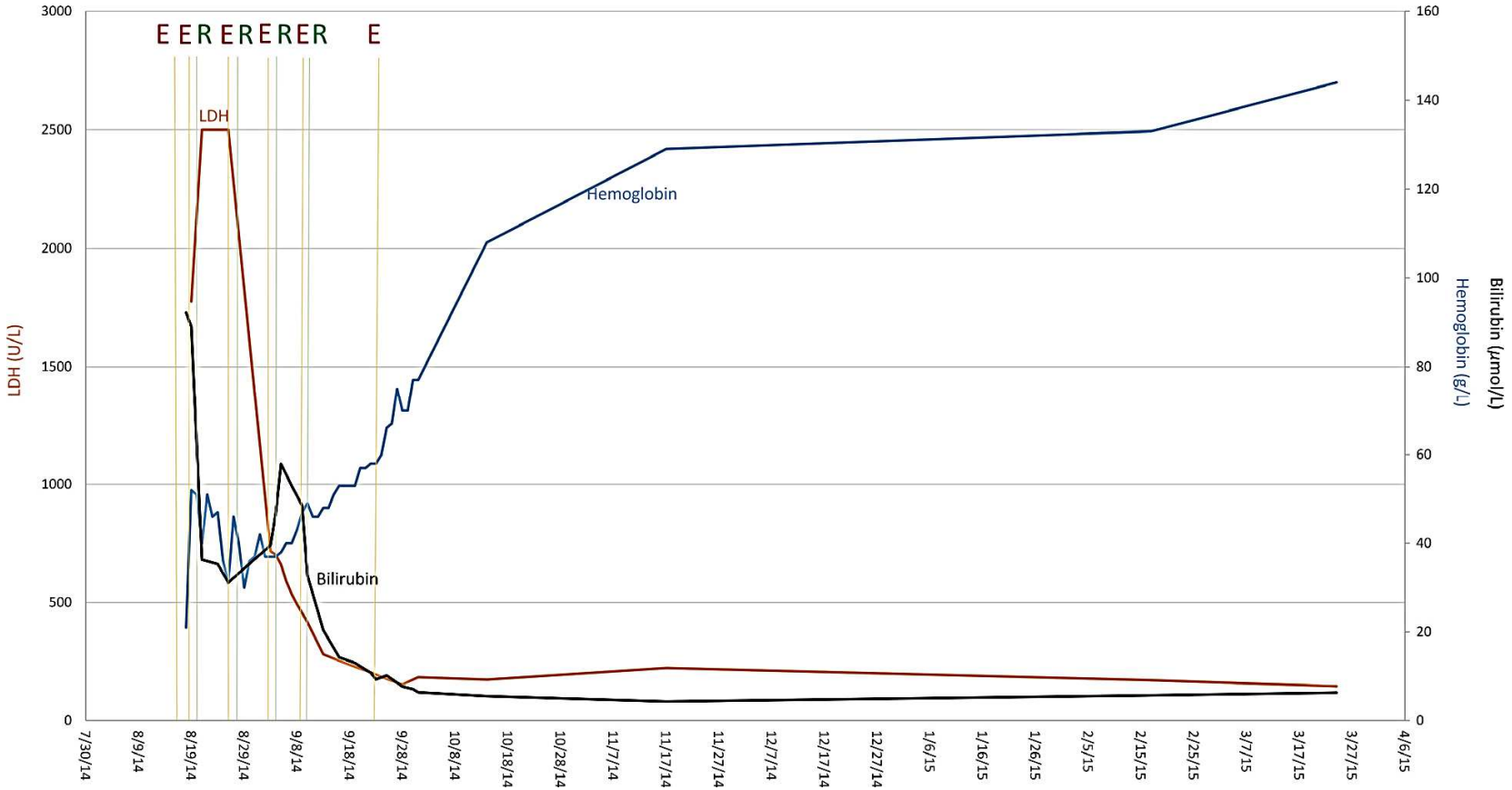
Open Access

CASE REPORT

Eculizumab as a bridge to immunosuppressive therapy in severe cold agglutinin disease of anti-Pr specificity

Roman Shapiro[1], Ian Chin-Yee[2] & Selay Lam[2]

[1]Department of Medicine, London Health Science Centre, Western University, London, Ontario
[2]Division of Hematology, London Health Science Centre, Western University, London, Ontario



Myasthenia Gravis

Physiopathologie de la myasthénie :

Auto anticorps anti-Récept acéthylcholine (aChR) :

- Dégradation accélérée et/ou blocage direct du récepteur,
- Destruction post synaptique par activation du Ct
  - dépots locaux C3b et C5b9,
  - atteinte moins sévère chez souris C3 déplet, $C5^{-/-}$, $C4^{-/-}$,
  - atteinte plus sévère chez $CD55^{-/-}$ ou $CD59^{-/-}$

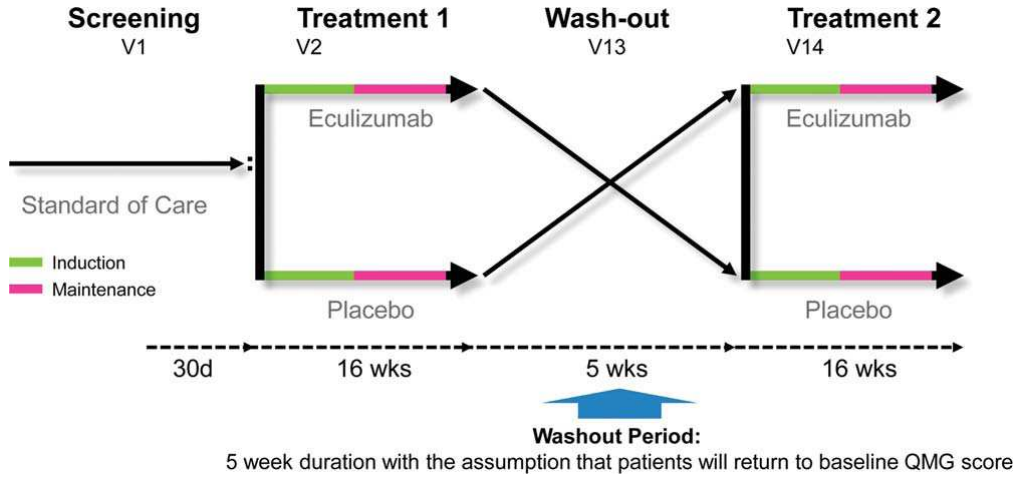
Modèle d'étude : Induction MG chez rat Lewis: Mab anti-AChR (McAb-3) +/- anti-C5

Résultats :

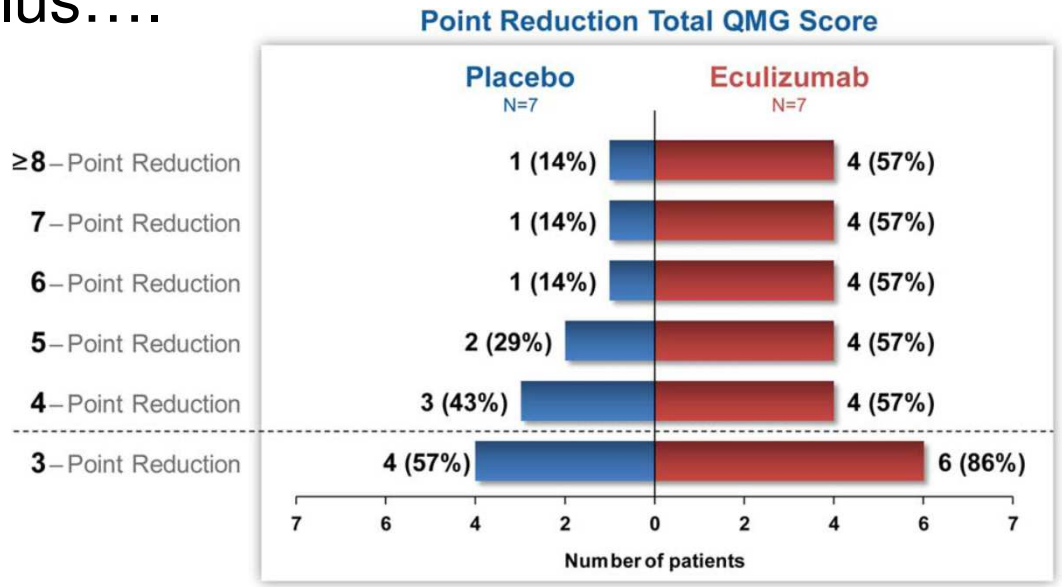
- diminution du score clinique et protection si pré-traitement
- diminution des dépôts de C9 mais pas de C3b
- Diminution des destructions histologiques et de l'infiltrat inflammatoire (Monocytes Macrophages)

Zhou,J Immunol, 2007,179:8562

A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis.



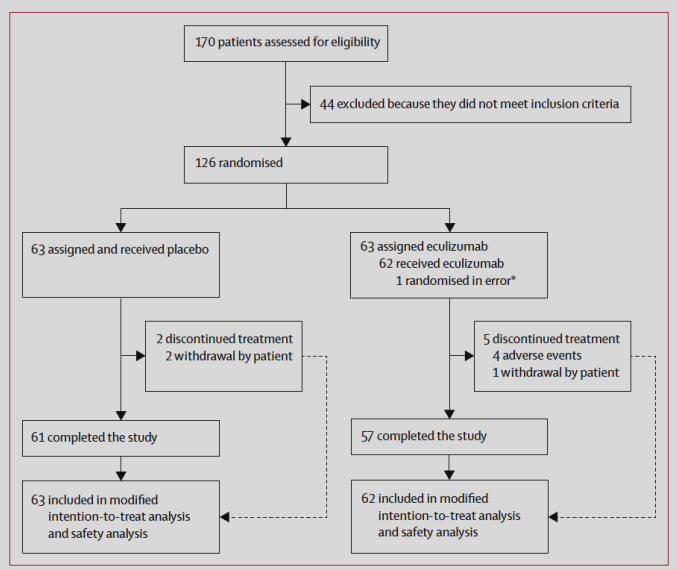
14 patients inclus….

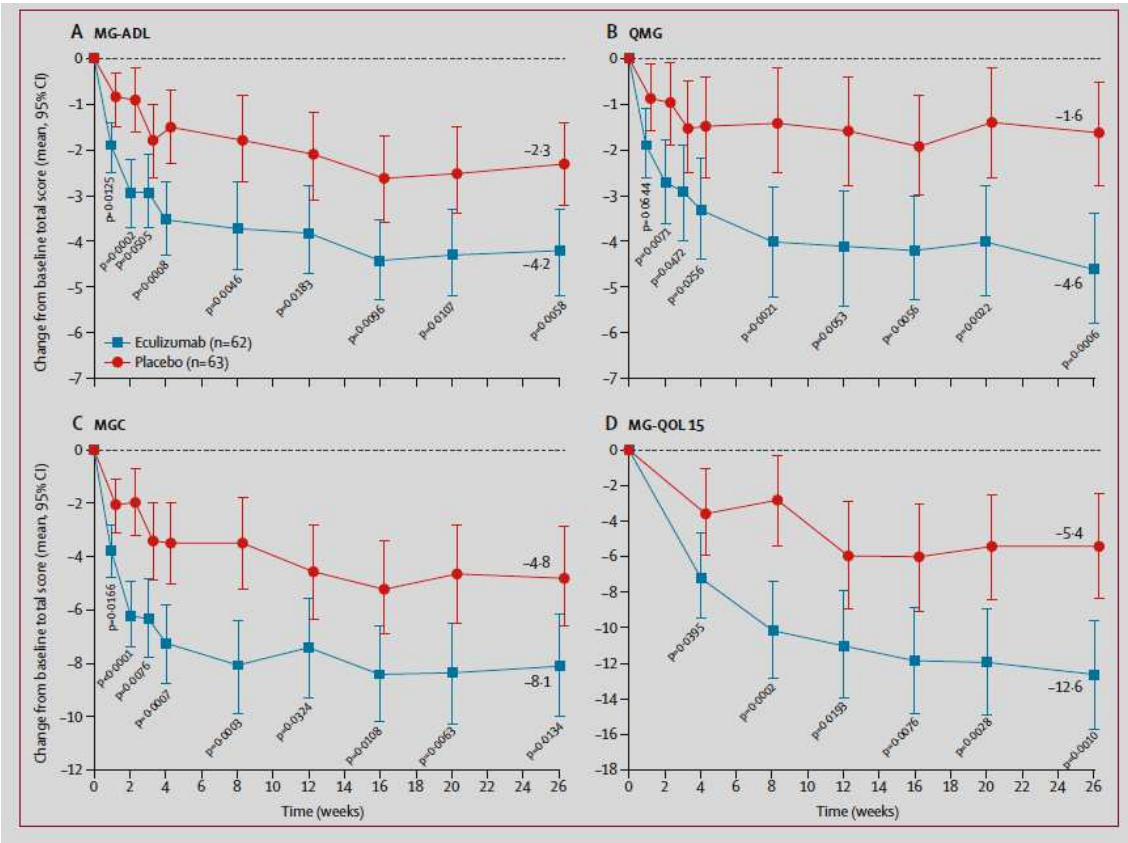


Howard J, Muscle Nerve. 2013 Jul;48(1):76-84

Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study

JF Howard, Lancet Neurol 2017; 16: 976–86

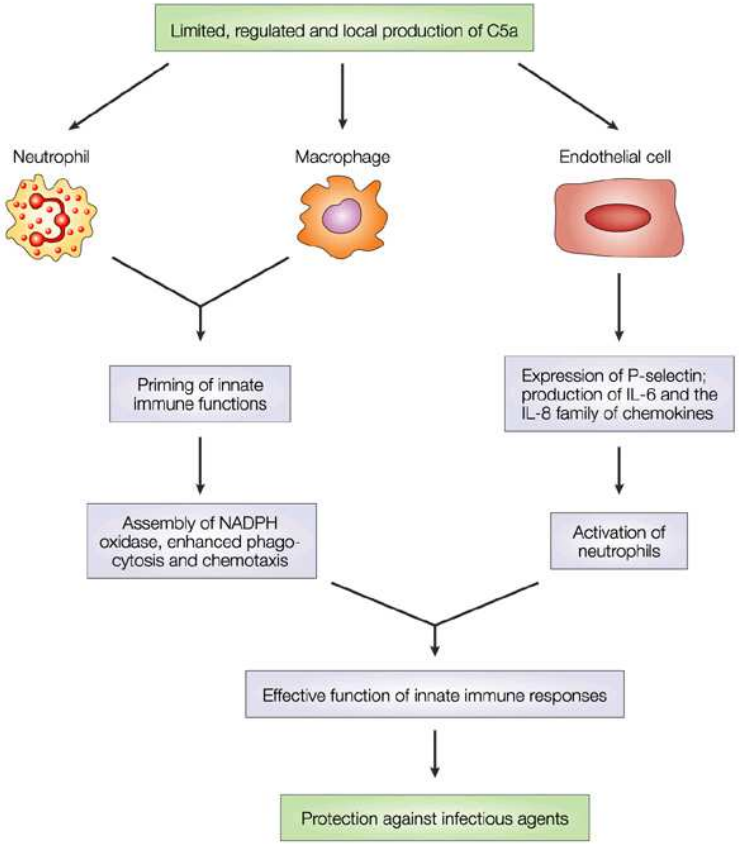


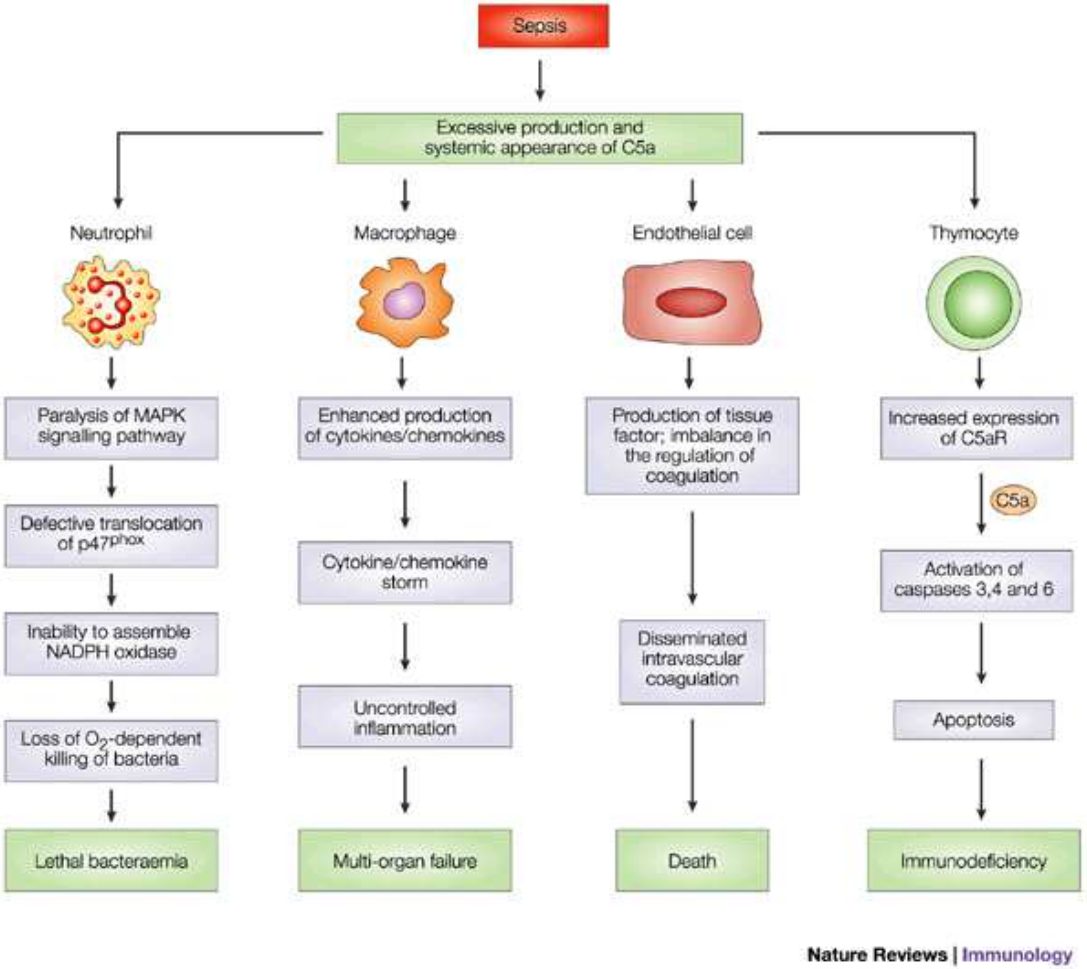


C5a : Récepteurs membranaires

Nom (murin)	**CD88 (C5aR)**	**C5L2 (Gpr77)**
Ligand(s)	C5a	C5a/C5aDesarg C3a/C3aDesarg
Signalisation	Protéine G	MAPK (HMGB1)
Phénotype KO	Protection from acute lung injury	Increased tissue injury

Rôle paradoxal de C5a dans le sepsis





Implication du Complément dans les vascularites à ANCA

Evidences expérimentales :

Johnson U,et al. Effects of granulocyte neutral proteases on complement components. Scand J Immunol **1976**.

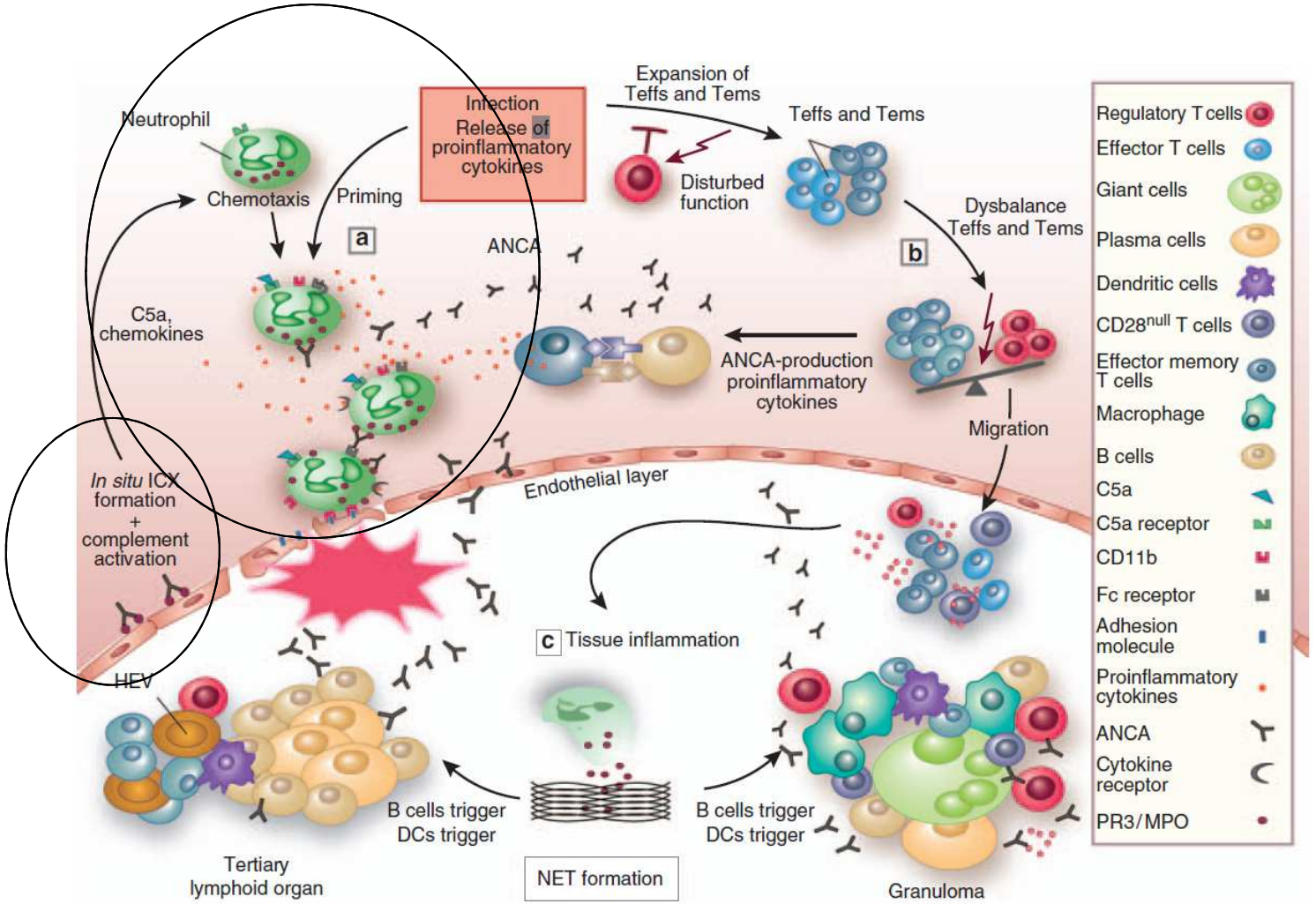
Vogt W. Complement activation by myeloperoxidase products released from stimulated human polymorphonuclear leukocytes. Immunobiology **1996**;

Xiao H, et al. Alternative complement pathway in the pathogenesis of disease mediated by anti-neutrophil cytoplasmic autoantibodies. Am J Pathol **2007**.

Schreiber A, et al. C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. J Am Soc Nephrol **2009**.

Huugen D, et al. Inhibition of complement factor C5 protects against anti-myeloperoxidase antibody-mediated glomerulonephritis in mice. Kidney Int **2007**.

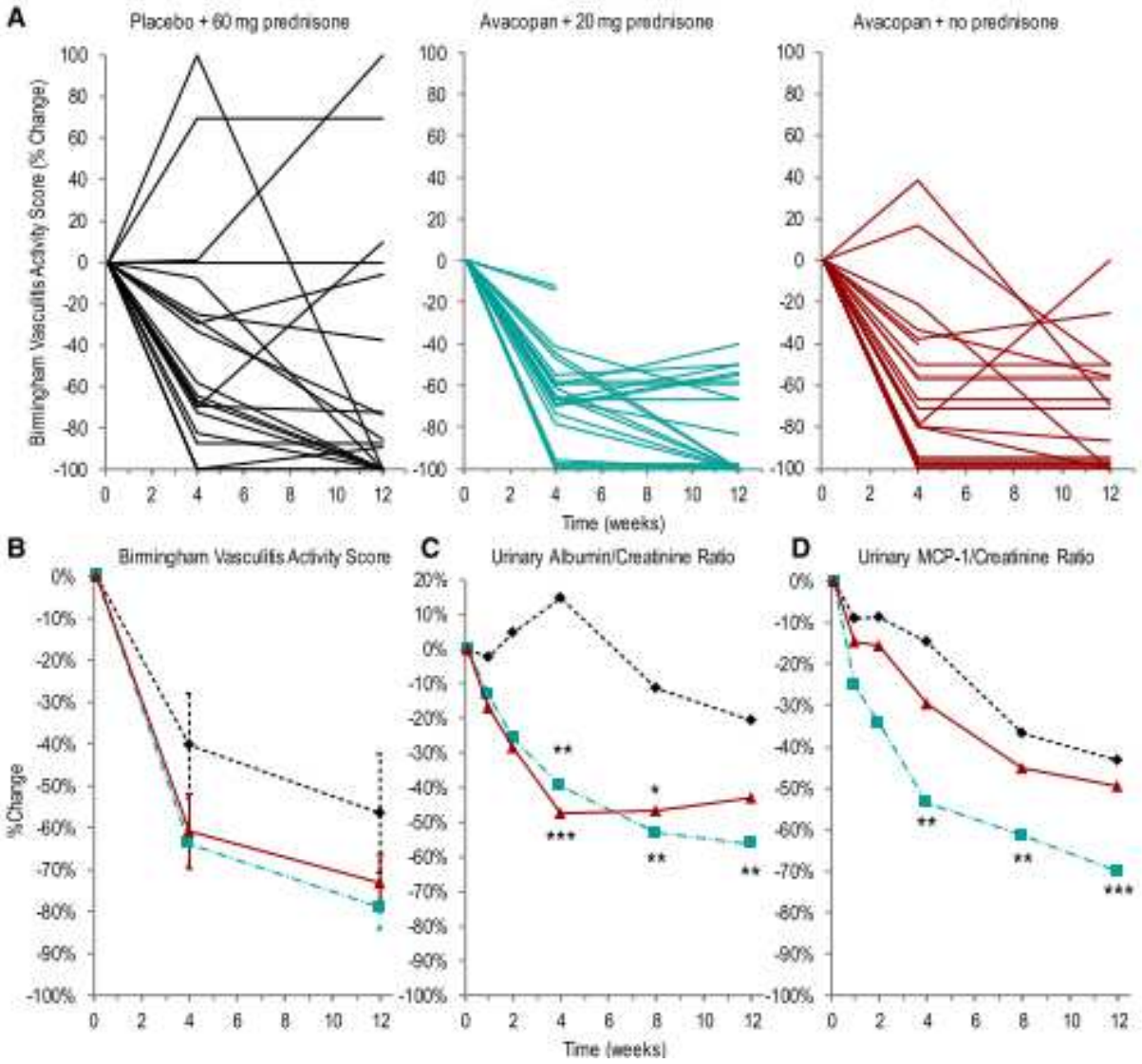
Implication du Complément dans les vascularites à ANCA



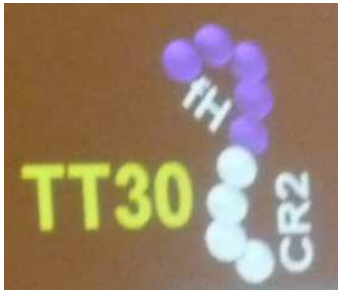
B Wilde, Kidney int, 2011

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

D Jayne,JASN, Apr 2017



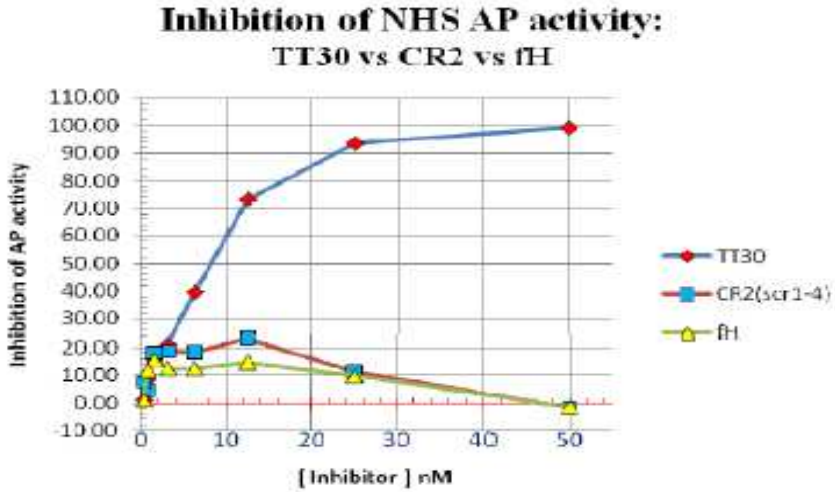
Ciblage voie alterne in situ
CR2-FH (TT30) (Taligen, Alexion)

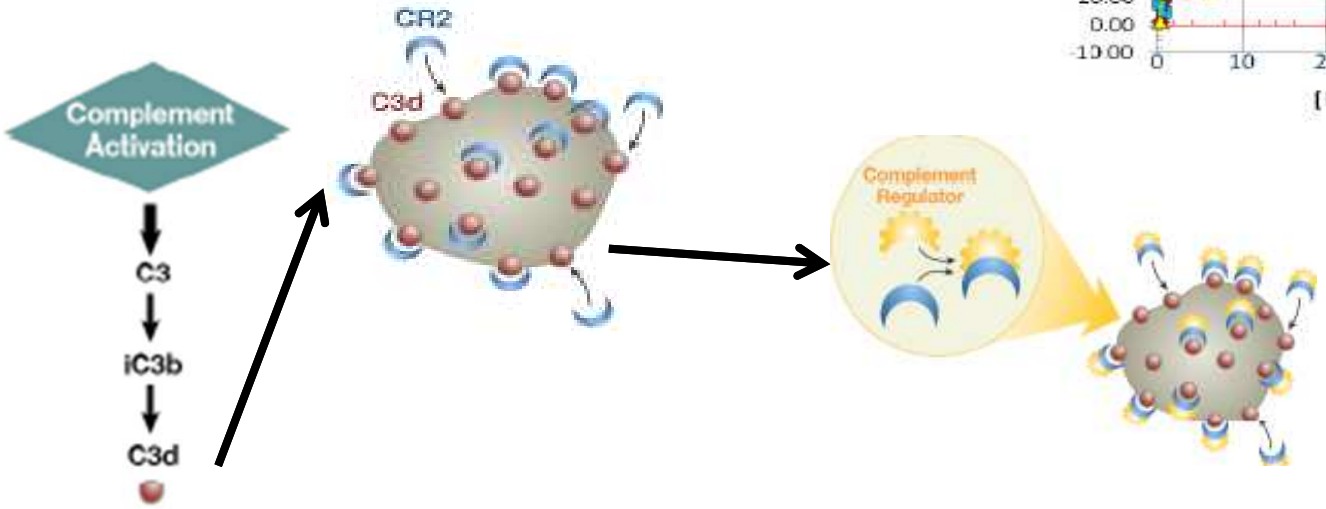


CR2

Factor H (fH)

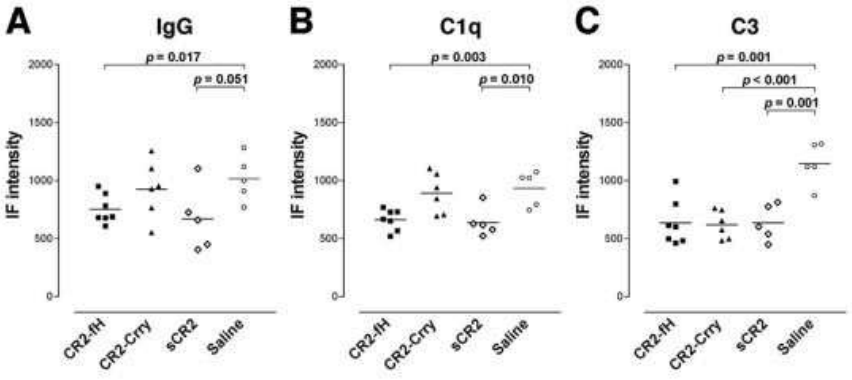
CR2-fH (TT30)

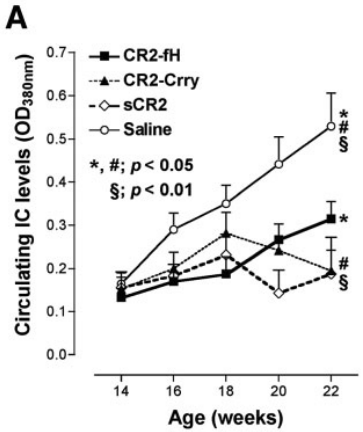


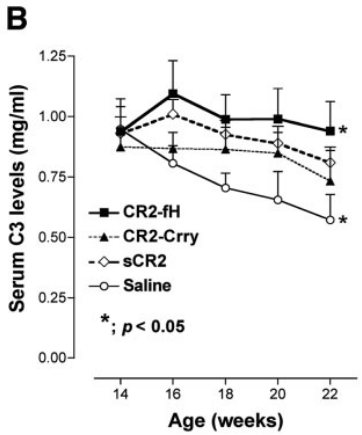


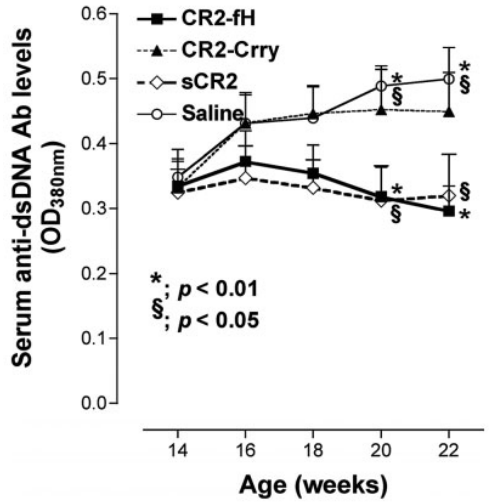
The Benefit of Targeted and Selective Inhibition of the Alternative Complement Pathway for Modulating Autoimmunity and Renal Disease in MRL/*lpr Mice*

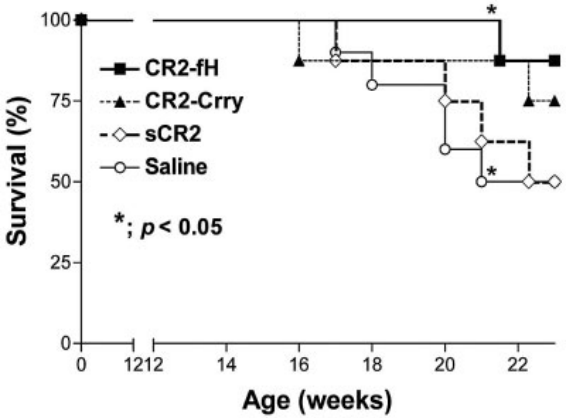
H Sekine, Stephen Tomlinson, ARTHRITIS & RHEUMATISM 63, 4, 2011, 1076–1085





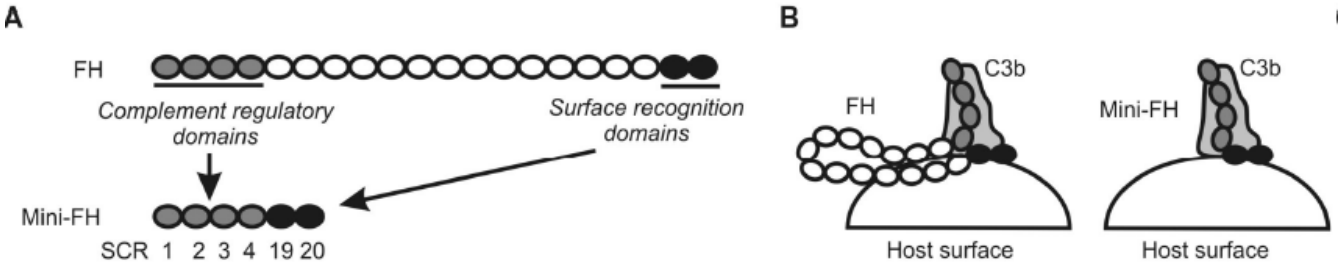


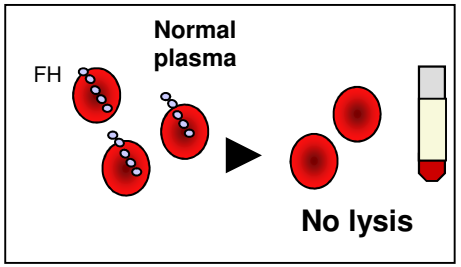


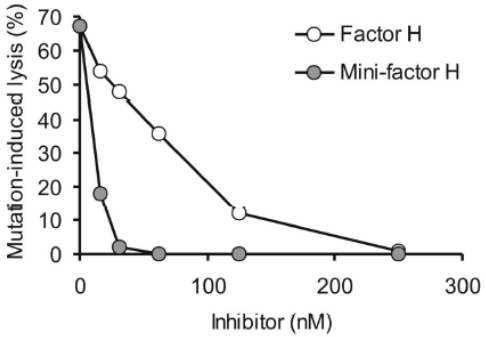


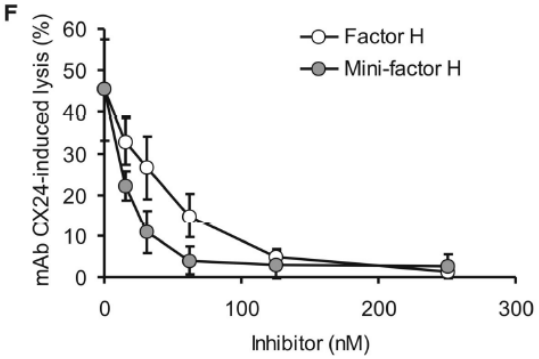
Efficacité fonctionnelle d'une protéine « mini-FH »

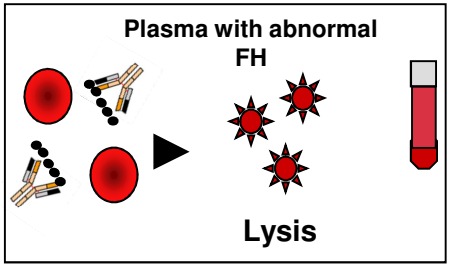
Hebecker et al, JI, 2013

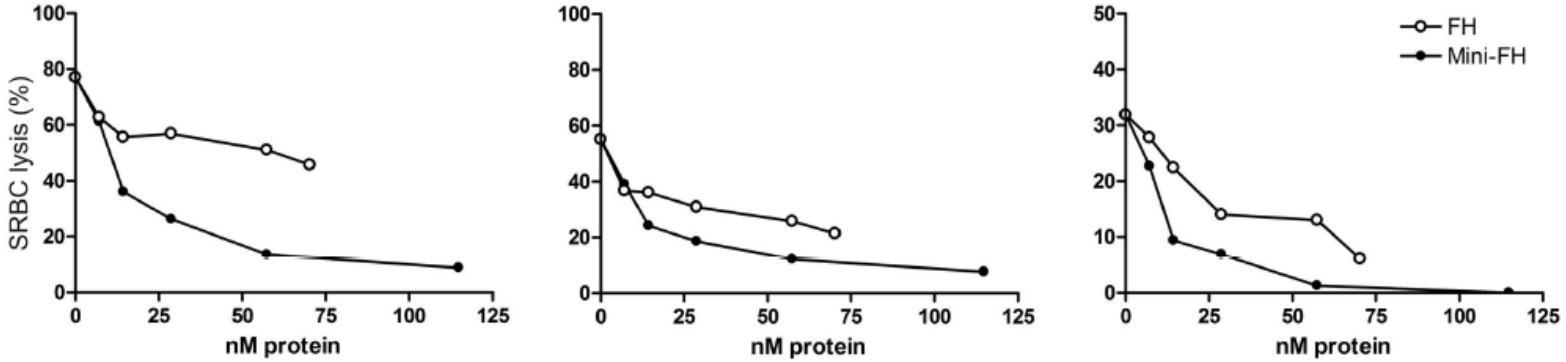








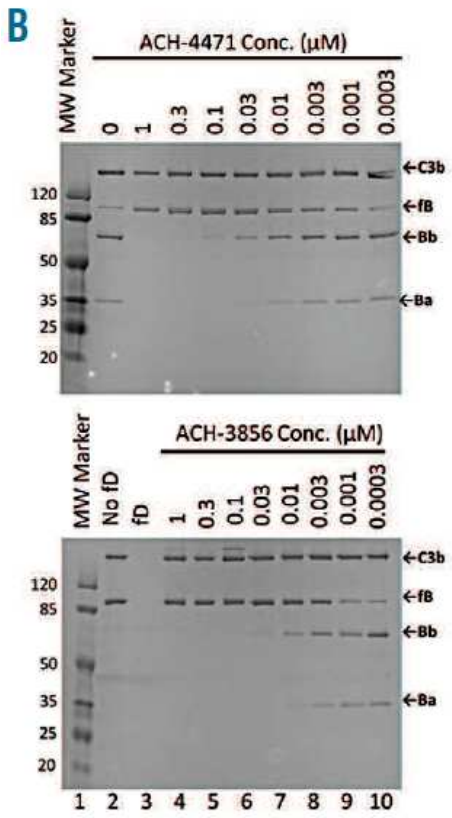




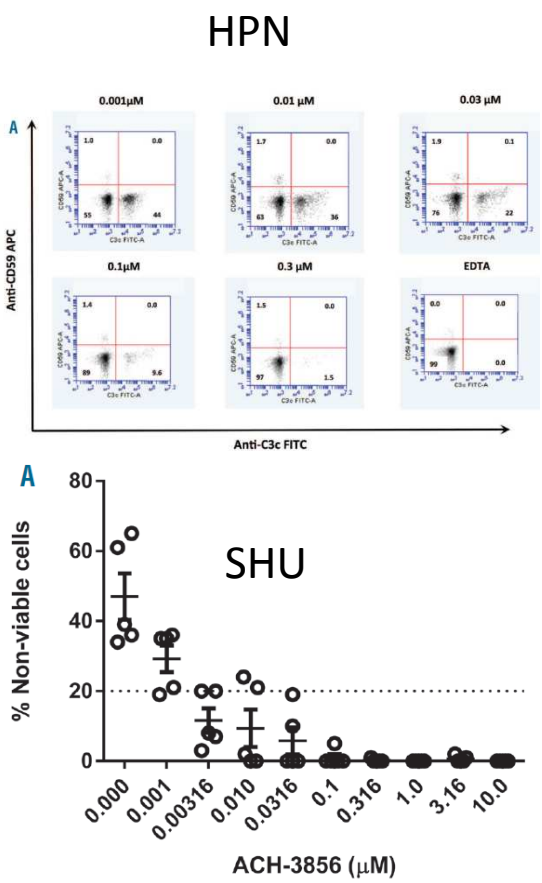
Samples containing anti-FH autoantibodies

Small-molecule factor D inhibitors selectively block the alternative pathway of complement in paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome

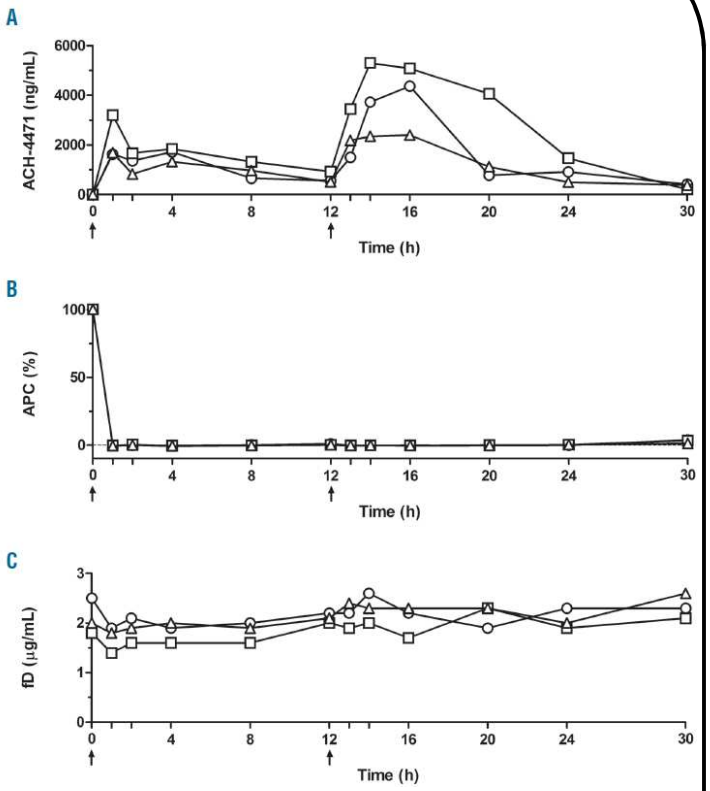
X Yuan, Haematologica 2017, 102(3):466-475



Effet sur protéines purifiées:
Blocage du clivage de C3



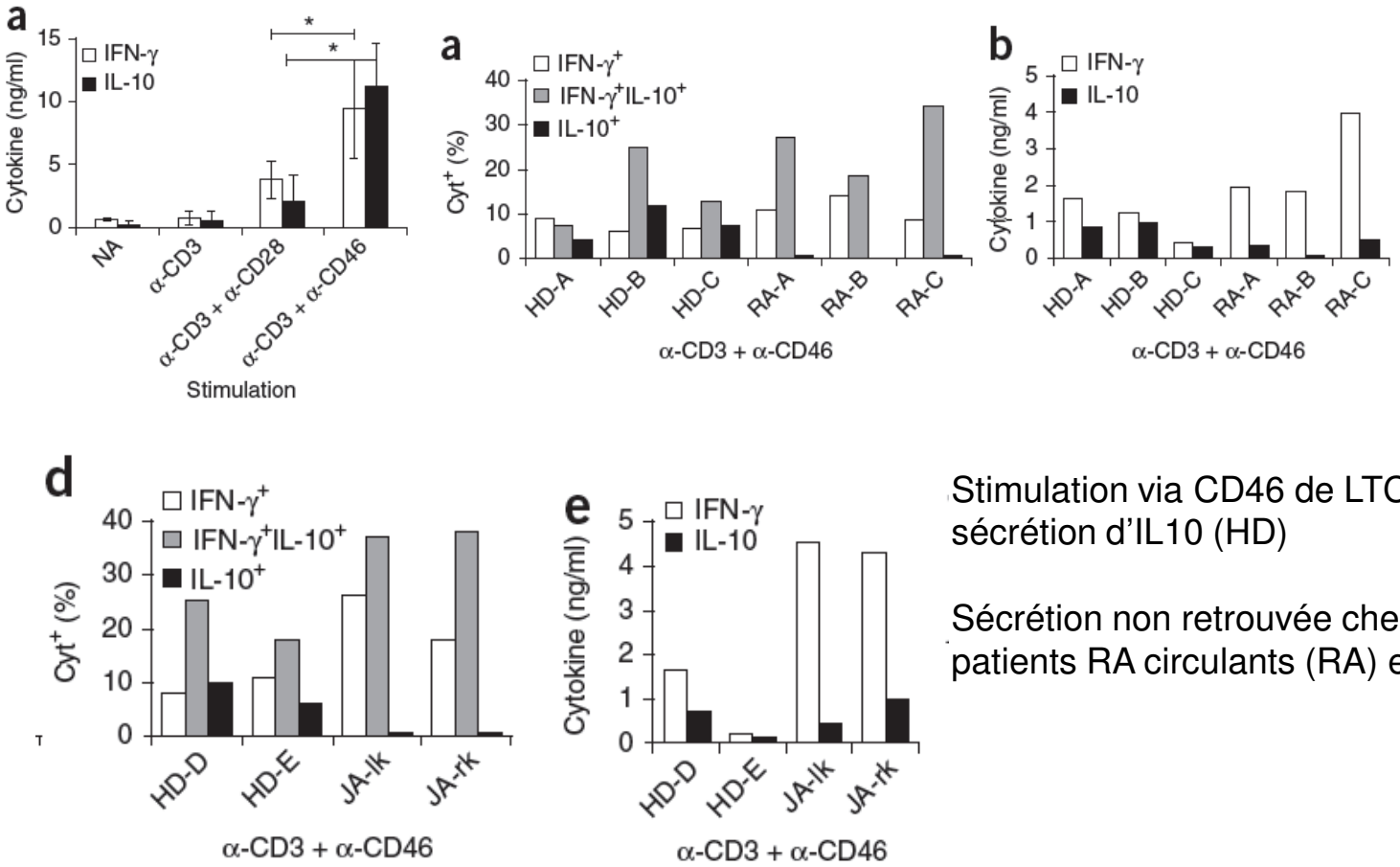
Effet sur échantillons humains:
Blocage de l'opsonisation par C3



Effet in vivo (primates):
Blocage de l'activation de la voie alterne par une prise orale (200mg/kg toutes les 12h)

Autre possibilité :
Cibler la réponse adaptative *via* le Complément?

Complement regulator CD46 temporally regulates cytokine production by conventional and unconventional T cells *Cardone, Kemper, Nature Immunol, 2010*

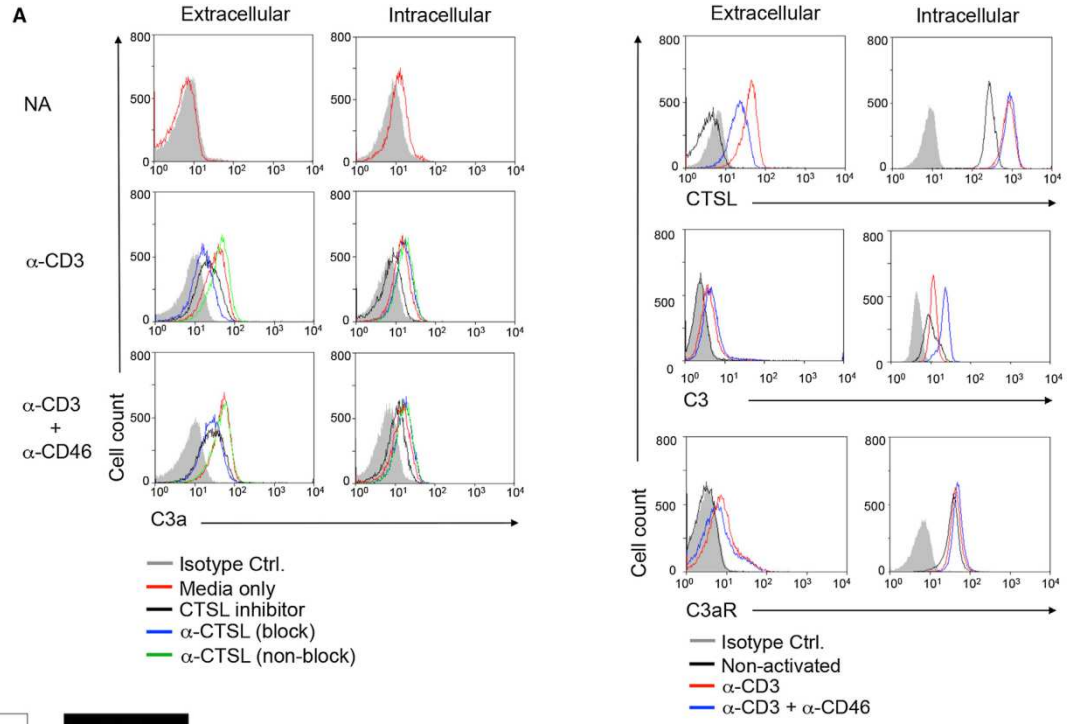


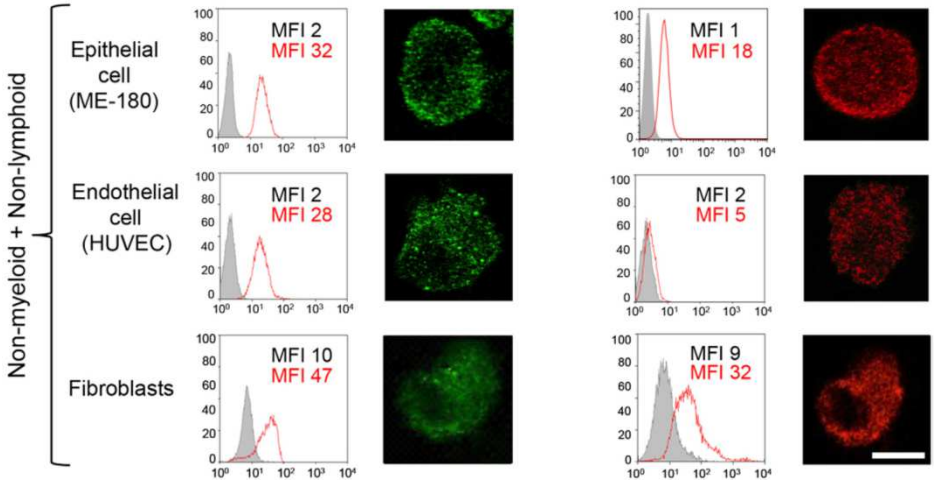
Stimulation via CD46 de LTCD4+ induit la sécrétion d'IL10 (HD)

Sécrétion non retrouvée chez les LT CD4 de patients RA circulants (RA) et articulaires (JA)

Intracellular Complement Activation Sustains T Cell Homeostasis and Mediates Effector Differentiation

Cathepsine L-Mediated Intracellular C3a Generation Is Required for T Cell Survival





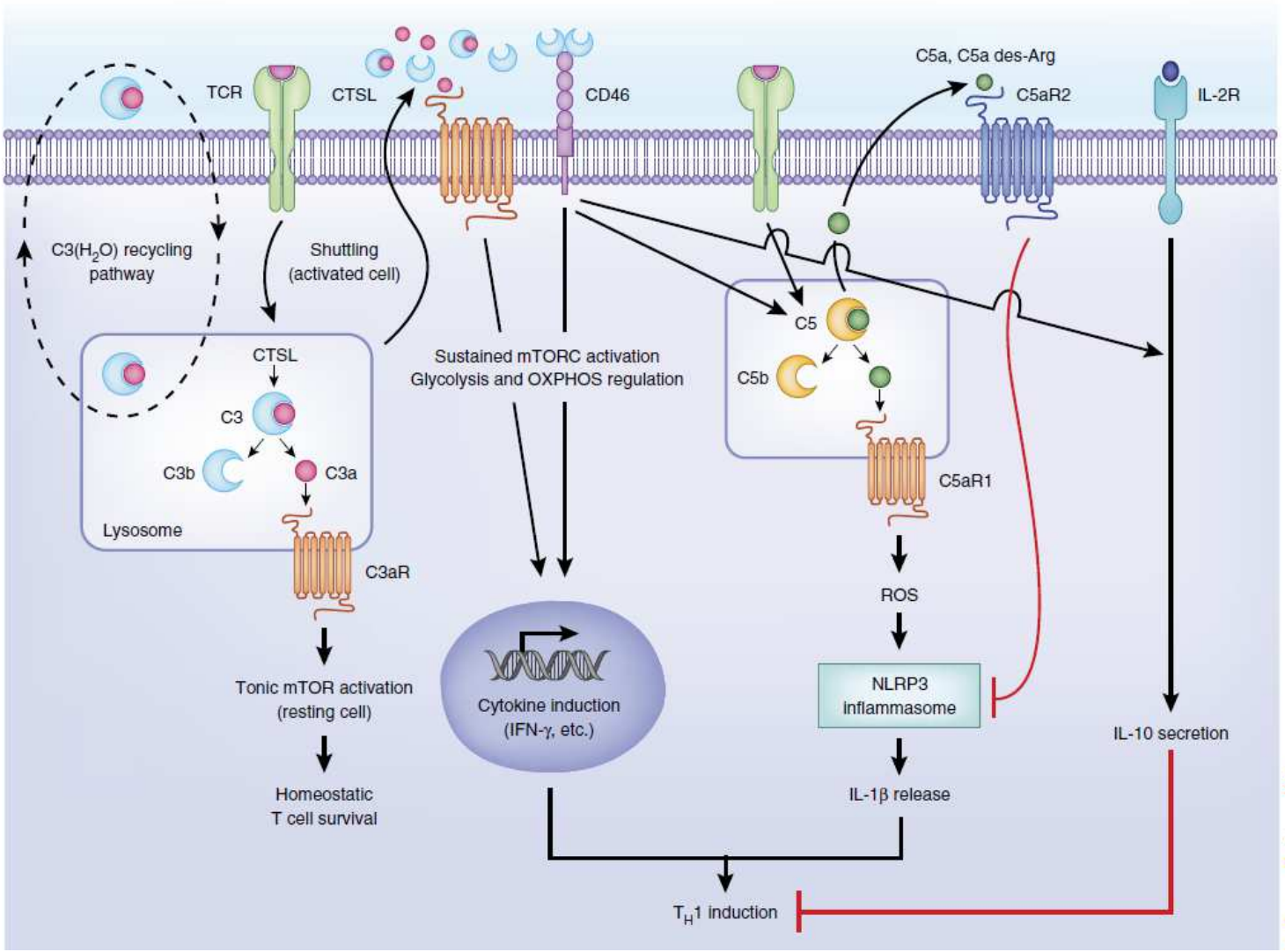
Intracellular C3 Activation Is Ubiquitous in Human Cells

Liszewski, Immunity. 2013 Dec 12;39(6):1143-57.

Novel mechanisms and functions of complement

nature immunology

George Hajishengallis[1], Edimara S Reis[2], Dimitrios C Mastellos[3], Daniel Ricklin[4] & John D Lambris[2]



The renaissance of complement therapeutics

D Ricklin, Nature Nephrol Rev, 2018