

Anti–Glomerular Basement Membrane Disease Subgroups and Novel Therapies

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Agenda

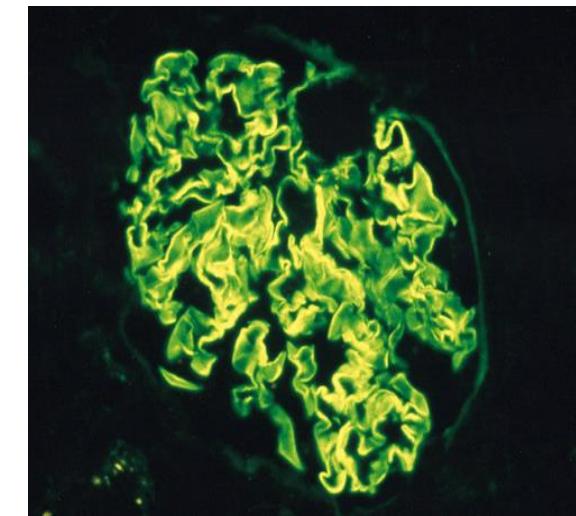
- Clinical presentation
- Atypical variants and overlap syndromes
- Pathogenesis
- Current treatment and prognosis
- New treatments

Anti-GBM disease – Goodpasture's disease

- Definition:
 - Renal and/or pulmonary small vessel vasculitis caused by anti-GBM antibodies
- Unspecific symptoms for a few weeks (months)
- Rapidly progressive glomerulonephritis or acute renal failure
- Pulmonary hemorrhage (before GN, concomitant or late)
- Subclinical lung engagement – anaemia, HRCT
- Incidence: 1.5 per million and year, men= women



Ernest William Goodpasture
1886-1960



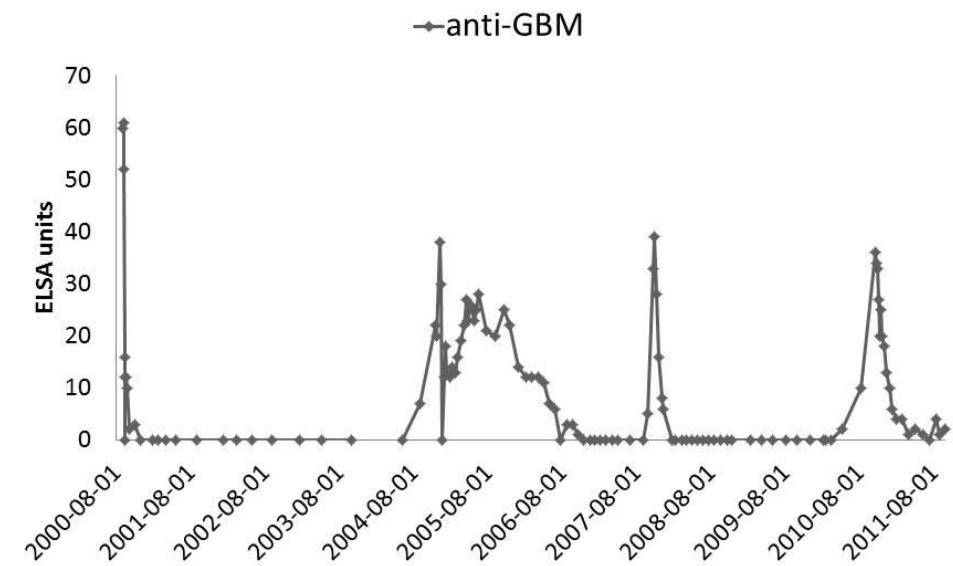
Rare variants and overlap syndromes

- Mild relapsing renal disease
- Overlap with membranous nephropathy
- Double positive ANCA + anti-GBM
- Sero-negative anti-GBM disease
- Isolated pulmonary disease
- IgG4- anti-GBM
- Post-transplant anti-GBM in Alport's syndrome

Mild relapsing glomerulonephritis

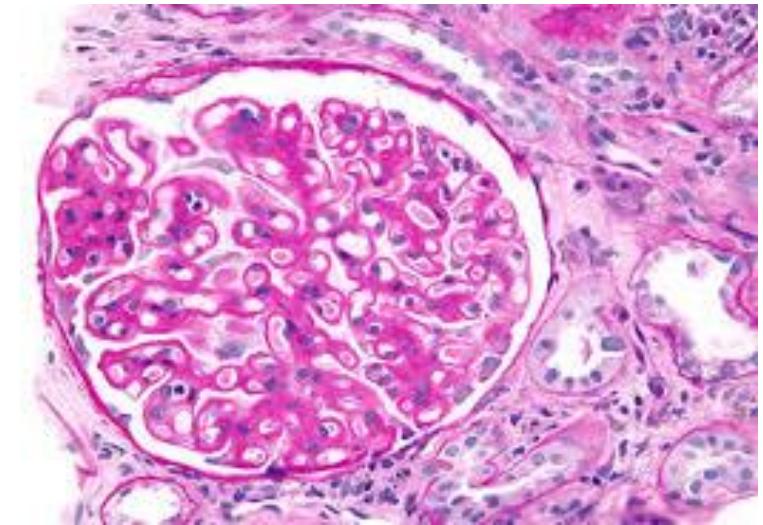
- Creatinine max 150 µmol/L
- Focal GN on biopsy
- 4 relapses over 15 years, with haematuria and rinsing creatinine
- Each time preceded by a rise in MPO-ANCA

Figure 1



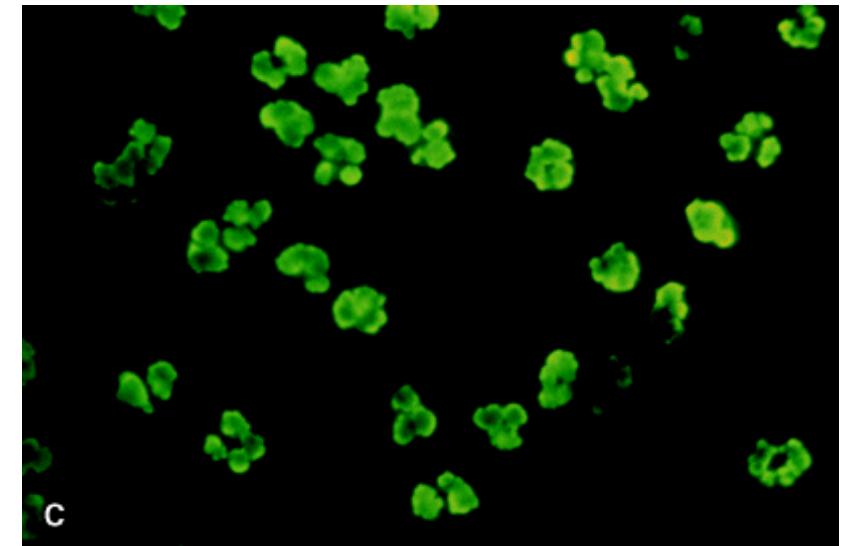
Overlap anti-GBM and membranous nephropathy

- Anti-GBM reacting with ColIV α 3(NC1)
 - Same specificity as “normal” anti-GBM
- No PLA2R-antibodies*
- More proteinuria – often nephrotic range
- Earlier diagnosis and better prognosis



Double positive ANCA-anti-GBM

- 20-45 % are MPO-ANCA positive
 - Or 2-5 % of MPO-ANCA have anti-GBM
- More prodromal symptoms
- Some have extrarenal vasculitis symptoms
- Older age at onset
- More chronic lesions
- Similar renal prognosis as single positive anti-GBM
- Similar risk of relapse as AAV



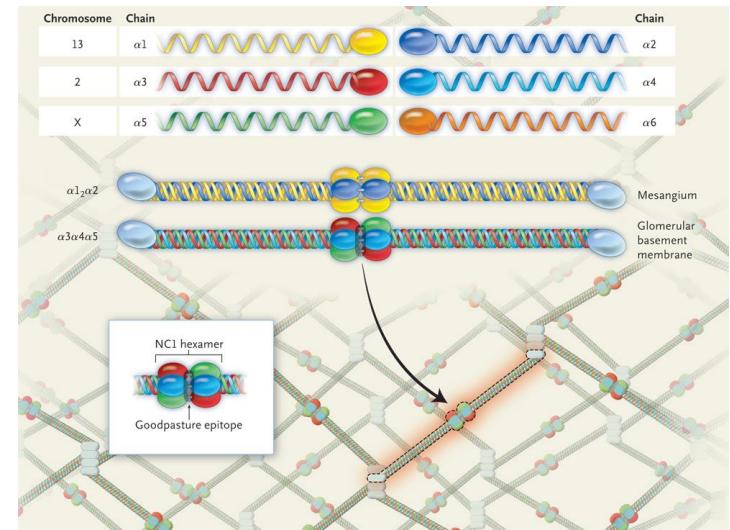
Sero-negative anti-GBM disease

- Different half-life of kidney bound and circulating antibodies
- Different specificity – detectable by IIF, western blot or by ELISA after different antigen preparations (hexamer)
- Anti-GBM of predominantly subclass IgG4

	Pat 1	Pat 2	Pat 3	Pat 4
Sex/age	F43	F22	F23	F18
Smoker	Yes	Yes	Yes	Yes
Lung haemorrhage	+++	+++	+++	+++
Max creatinine µmol/L	88	194	477	81
Relapse	Yes	no	no	Yes

Post-transplant anti-GBM disease

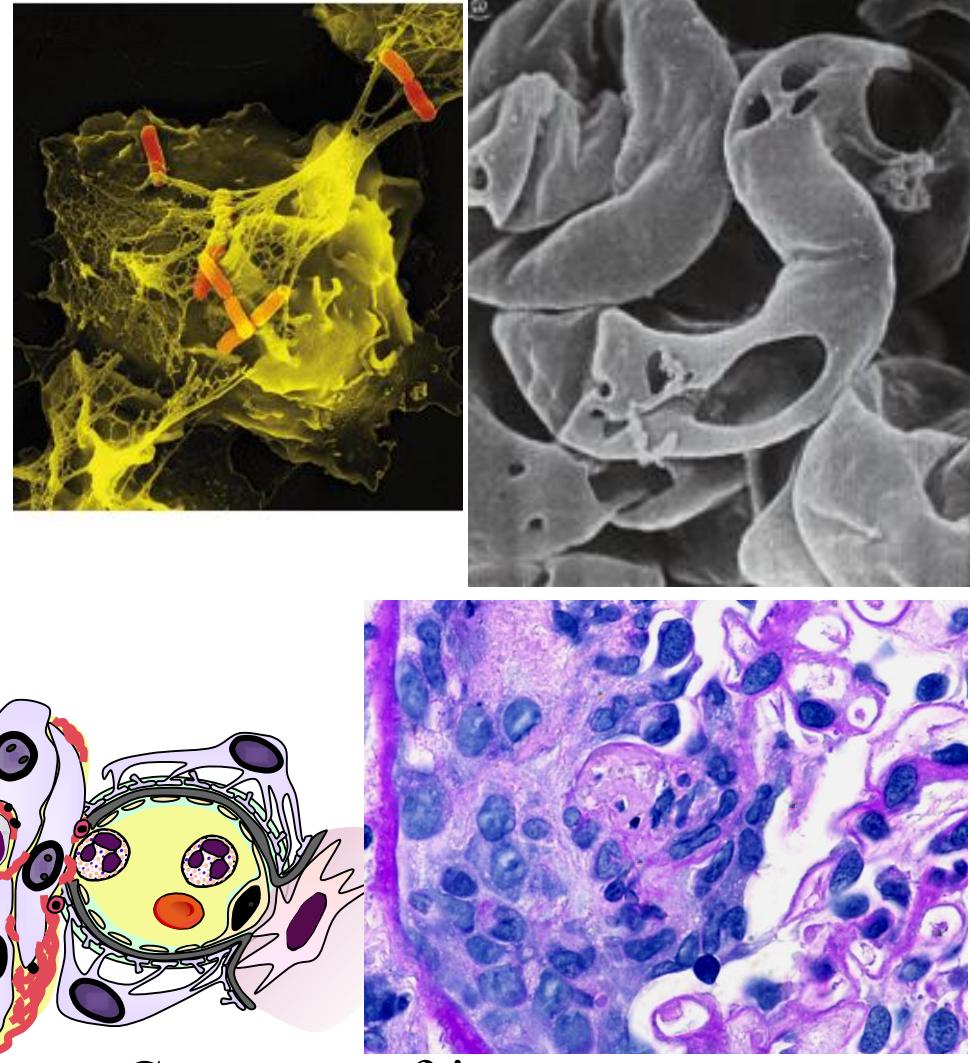
- Alloantibodies to antigen not experienced before
- Boys with X-linked disease and recessive Alport only
- Mainly anti-col IV(α 5), but epitope spreading occurs
- Normal ELISA can miss alloantibodies
- Large deletions increases the risk
- Clinical disease (RPGN) uncommon, <1% in recent report
- Subclinical disease – linear IF on protocol biopsy relatively common (30%?)



Cecil Alport 1880-1959

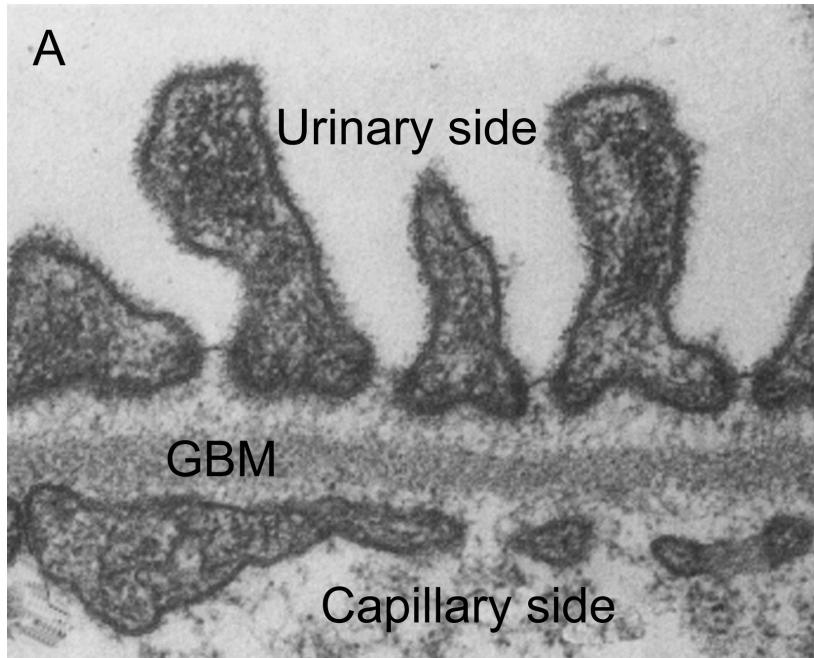
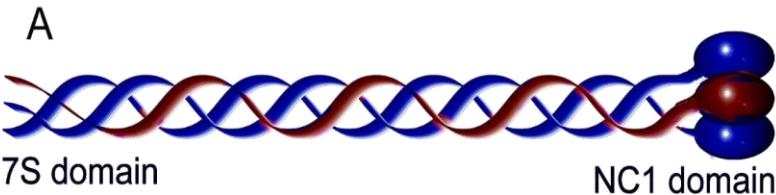
Pathogenesis of anti-GBM disease

- Binding of IgG autoantibodies to the GBM
- Activation of the classical complement pathway and recruitment of neutrophils through Fc and complement receptors
- Neutrophil degranulation and NET-os
- Enzymatic degradation fo the GBM
- Bleeding into Bowman's space
- Coagulation and macrophage infiltration
- Cellproliferation (crescents)
- Resolution and scarring

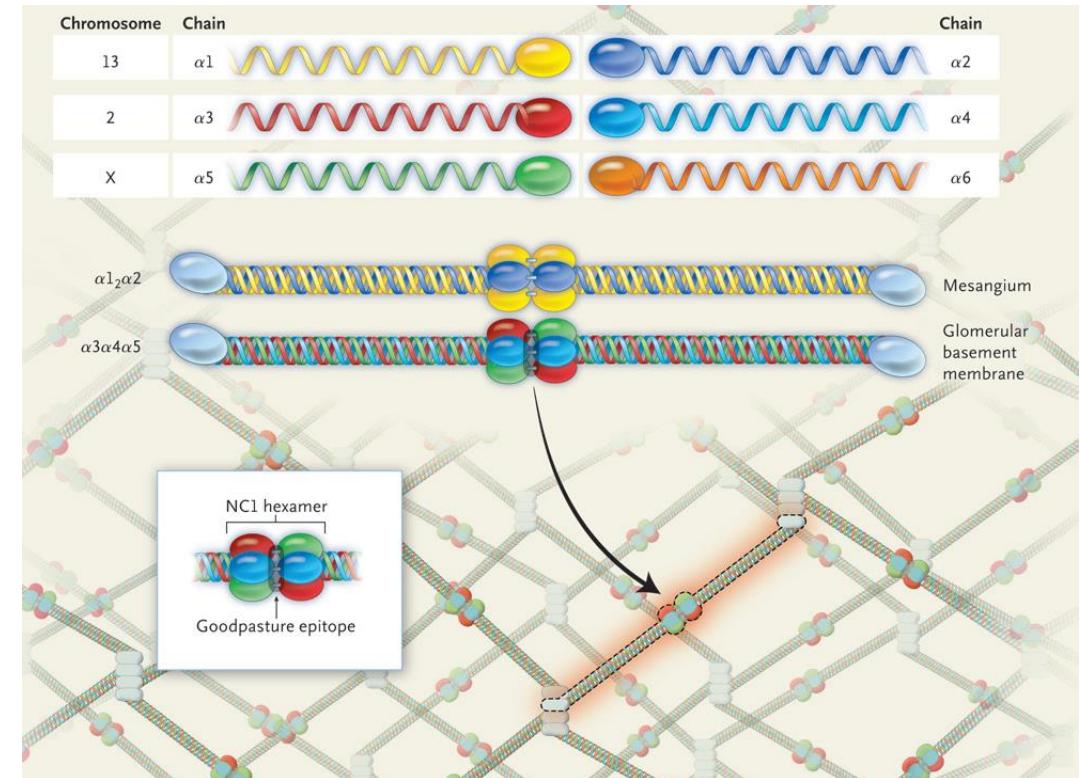


Crescentnephritis

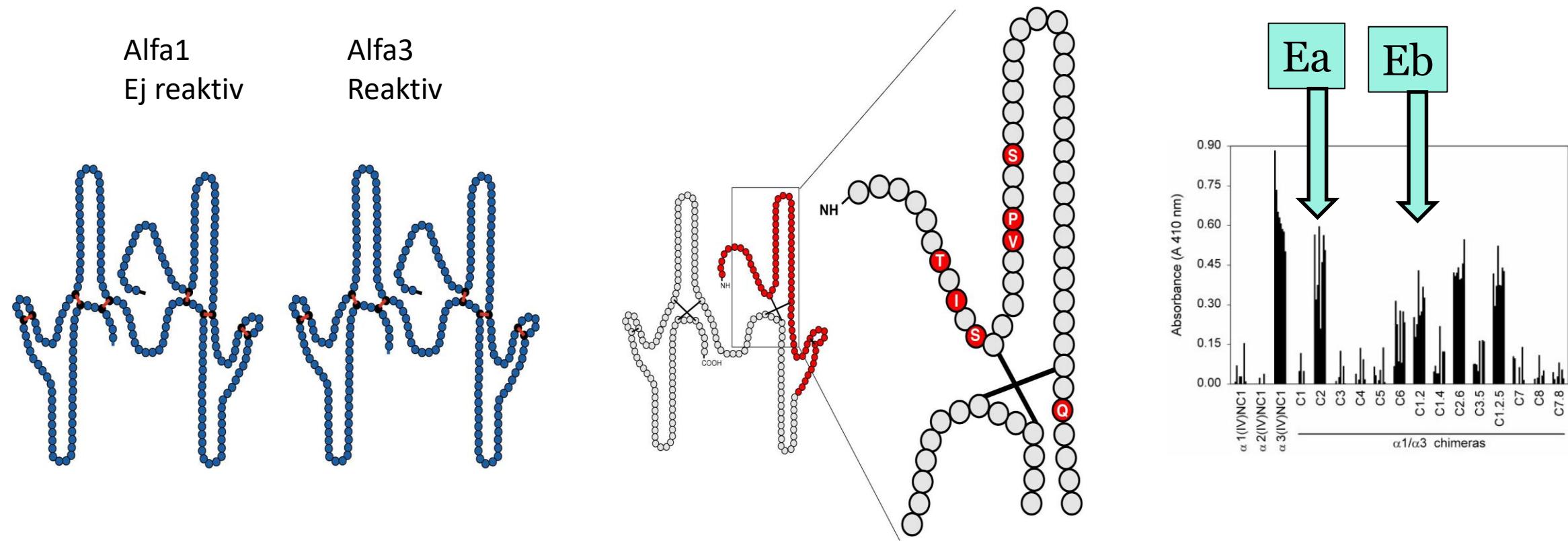
The target antigen Type IV-collagen



- 3 alpha-chains in each molecule
- 2 molecules bind to the C-terminal
- 4 molecules bind via the N-terminal
- 6 different types of alpha-chains



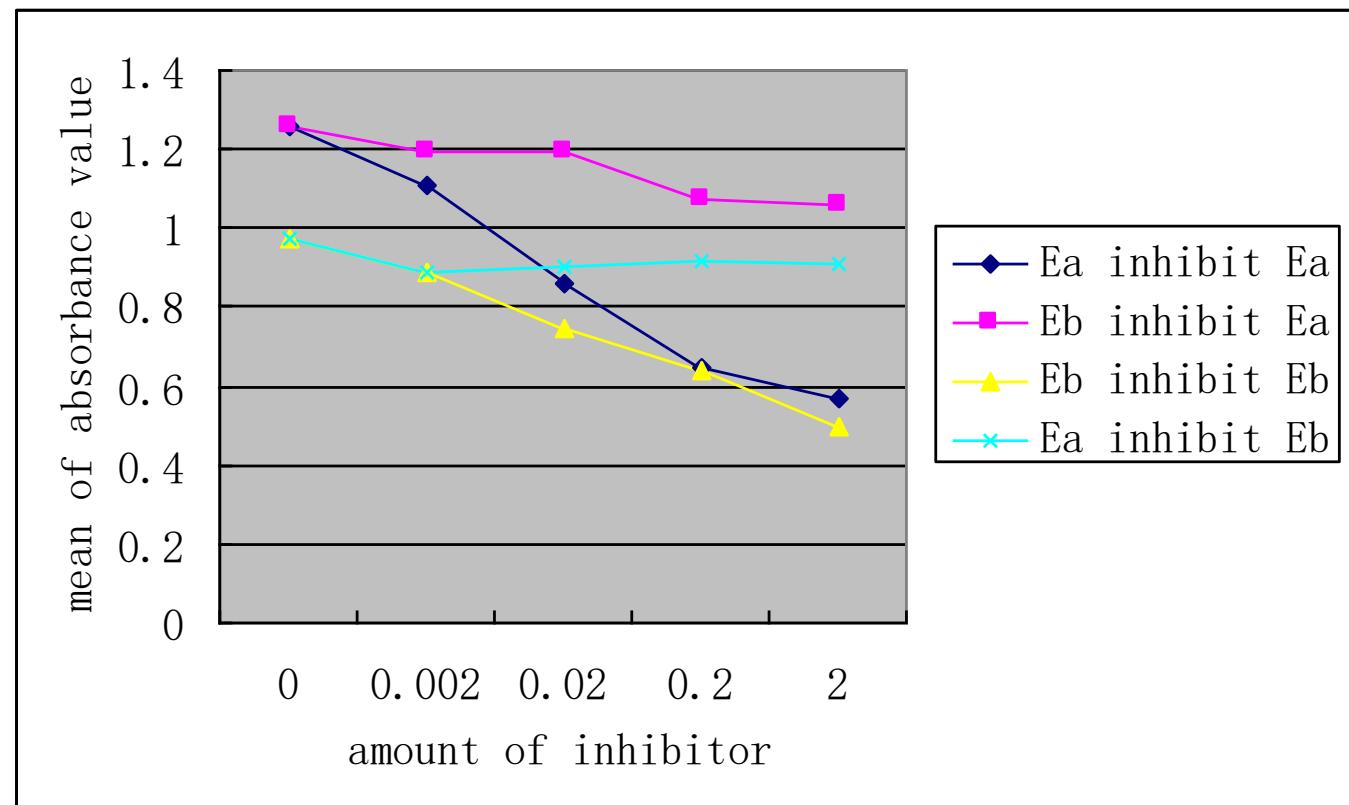
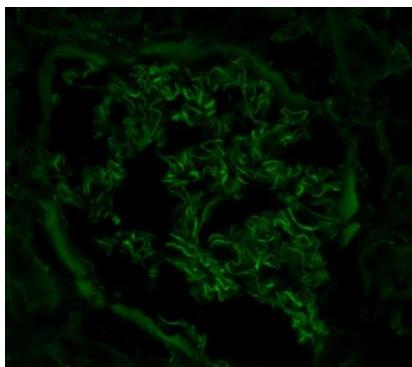
The B-cell epitope



Natural IgG autoantibodies to GBM



- Present in the sera from healthy persons
- Purified by affinity chromatography
- Produce a linear IIF pattern on human glomeruli
- Reacts with NC1 domain of the $\alpha 3$ -chain of type IV collagen
- Highly specific for either Ea or Eb

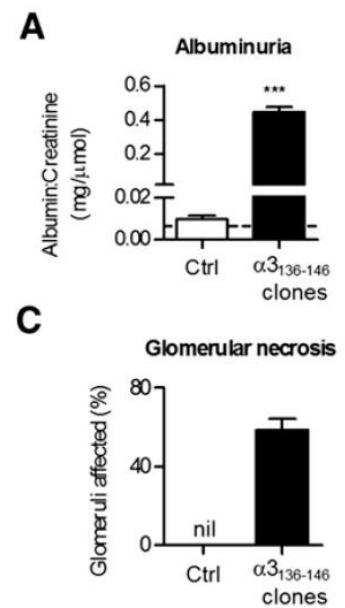
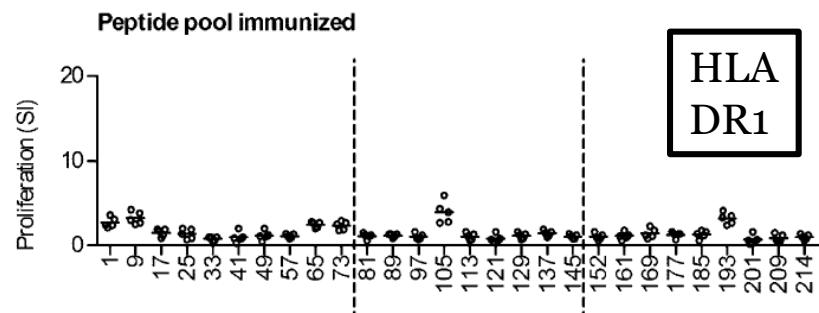
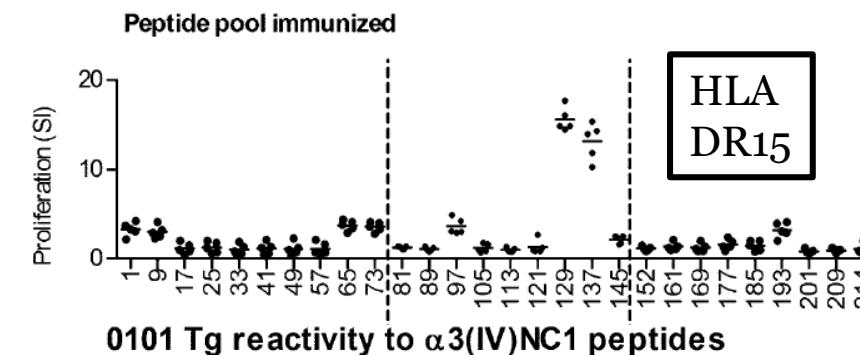


T-cells epitope (presented by HLA-DR)

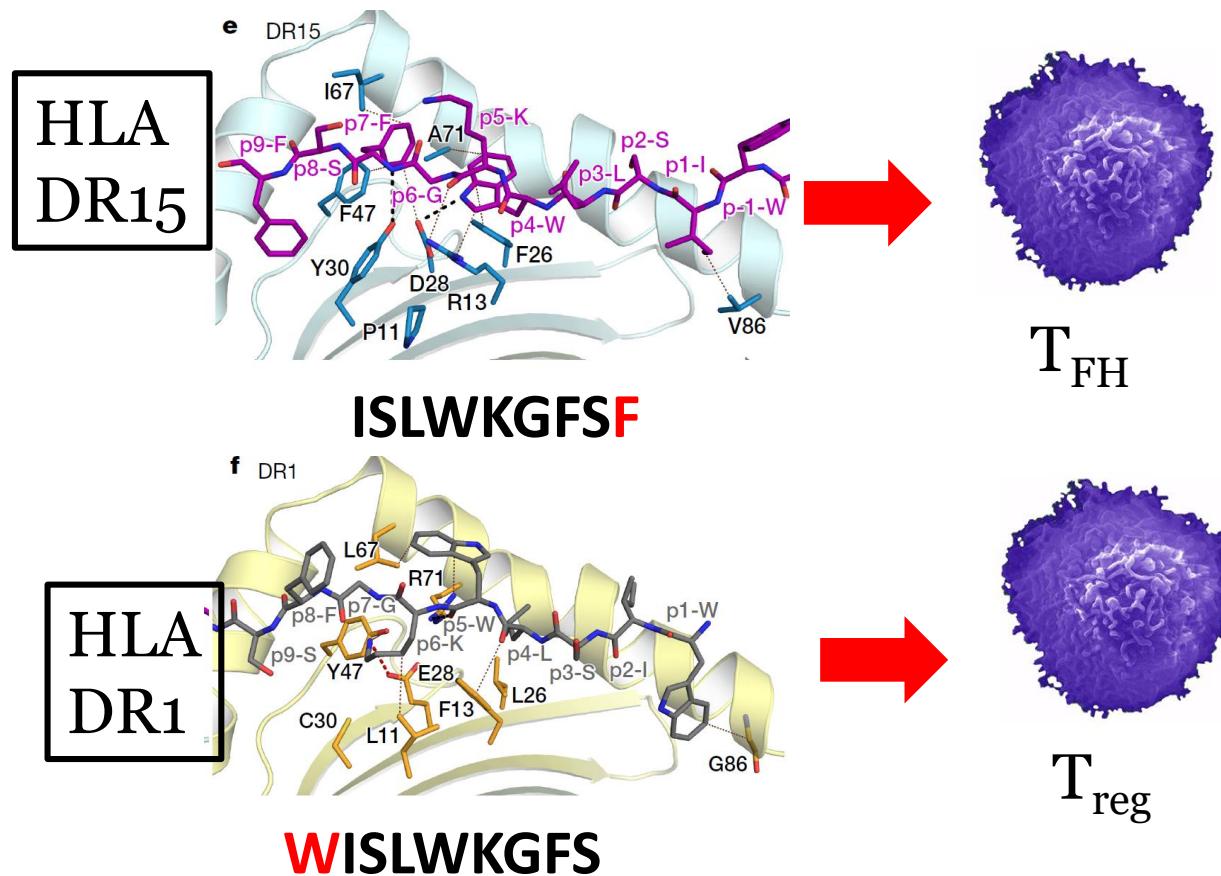
HLA-DRB1	Patients	Controls	Relative risk
0101	6%	20%	0.26
0301	22%	24%	0.9
0401	43%	41%	1.06
0701	5%	25%	0.15
1101	4%	11%	0.3
1201	6%	3%	2
1501	74%	28%	7.4

Transgenic mice with human HLA-DR immunized with $\alpha 3$ NC1 peptides

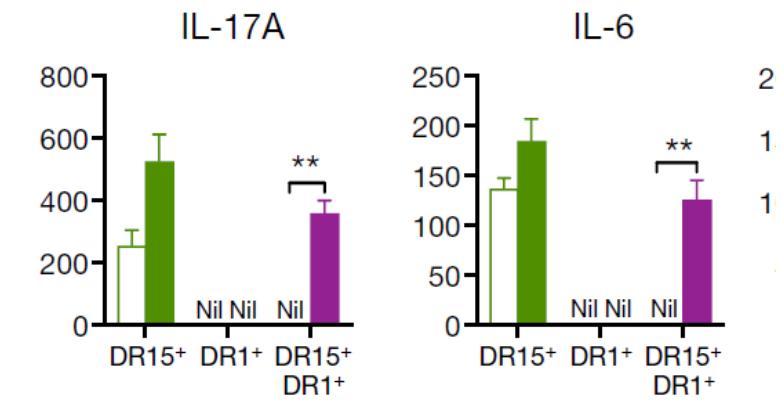
A 1501 Tg reactivity to $\alpha 3$ (IV)NC1 peptides



HLA-DR and peptide interaction drives T-cell reactivity



	Wild type	Treg depleted
DR1/DR1	No disease	No disease
DR1/DR15	No disease	Severe GN
DR15/DR15	Severe GN	Severe GN



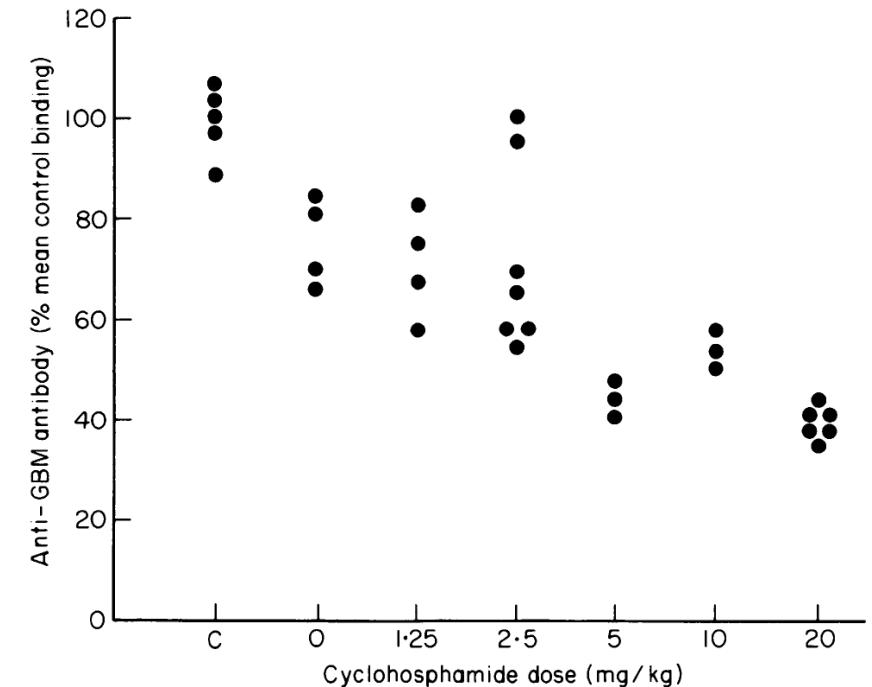
Treatment of anti-GBM disease

- Pulse-doses of corticosteroids
- Cyclophosphamide
- Plasma exchange
- Supportive care as needed with dialysis and mechanic ventilation



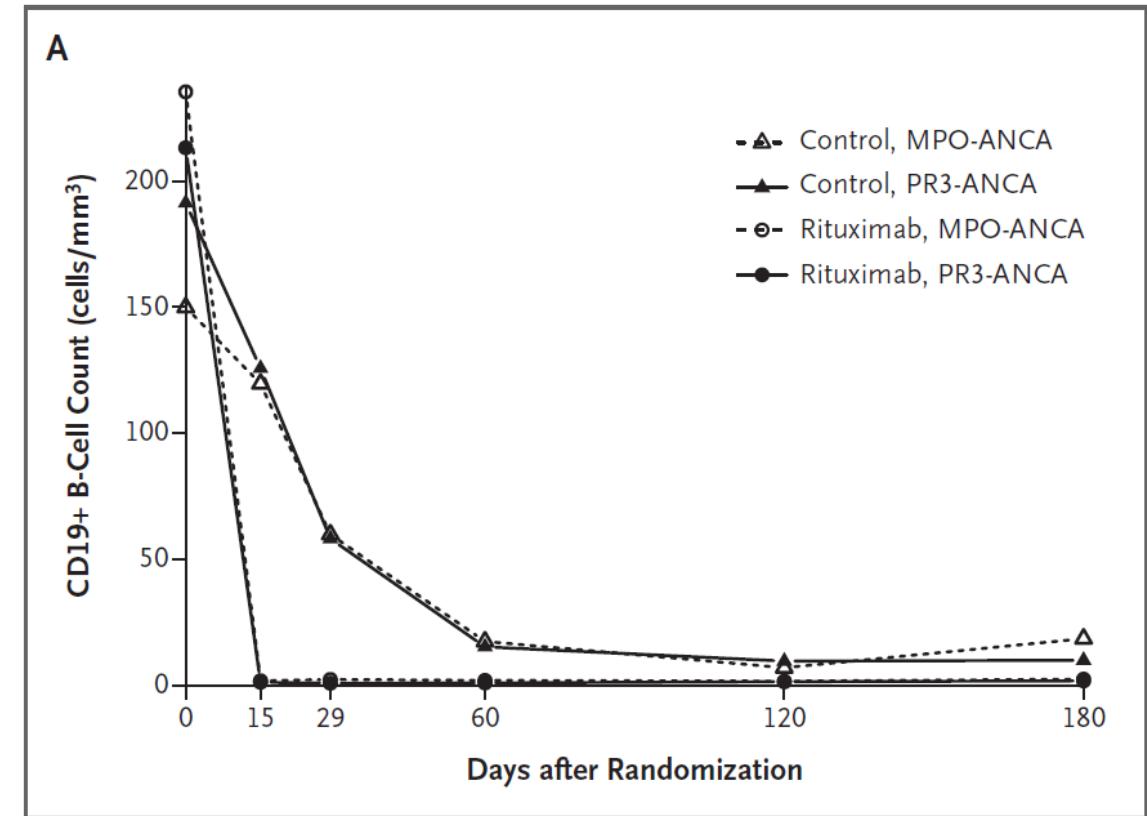
Autoantibody production and treatment

- Normal half life of IgG is 21 days
- Plasma cells can be short-lived or long lived
- CYC stop recruitment of new plasma cells
- B cells sensitive to CYC
- But also PMN, monocytes, T cells are affected



Rituximab vs Cyclophosphamide

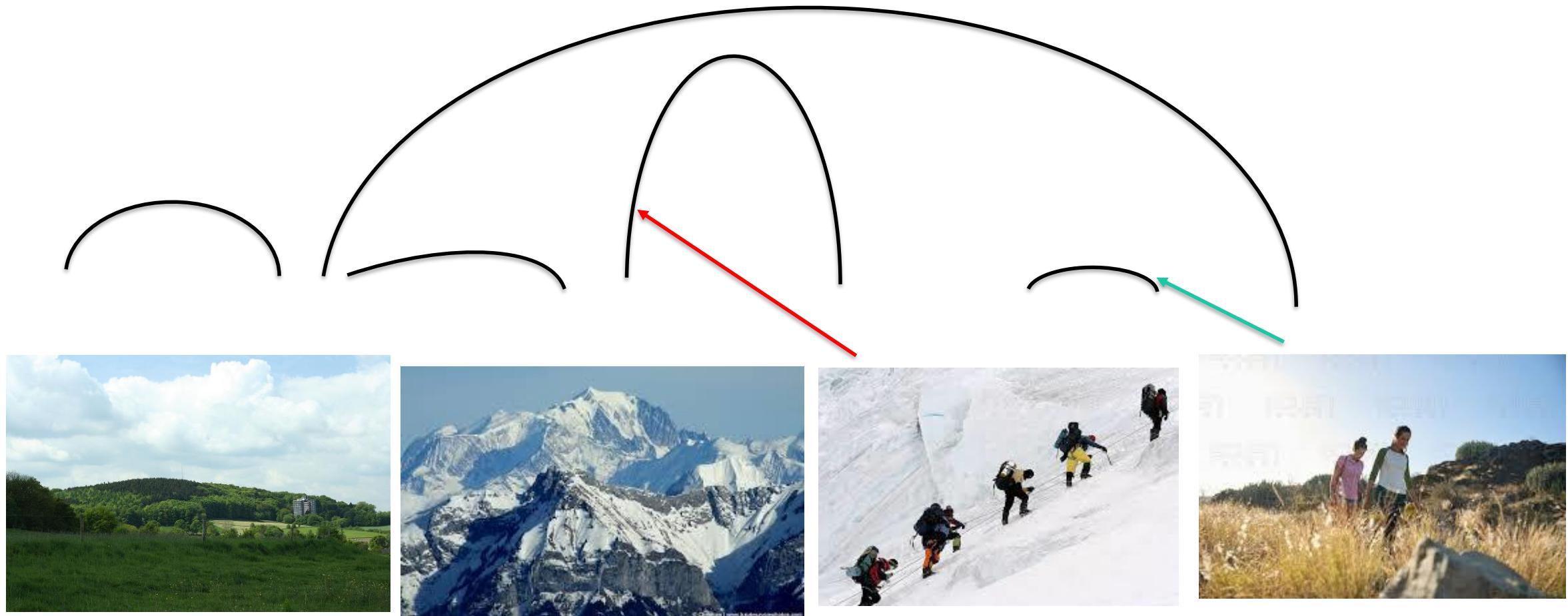
- Faster decline of B cells
- Faster disappearance of ANCA
- Less data in anti-GBM disease



Dosing of plasma exchange in anti-GBM disease

- Daily exchanges of 1,5 plasma volumes
 - On demand:
 - Daily until a non-toxic level (or negative result) is achieved
 - Tailored according to anti-GBM levels to stay below that level
 - According to a fixed schedule:
 - 6-7 exchanges are given as a series
 - Clinical response determines what is done afterwards
 - Not adjusted according to anti-GBM levels

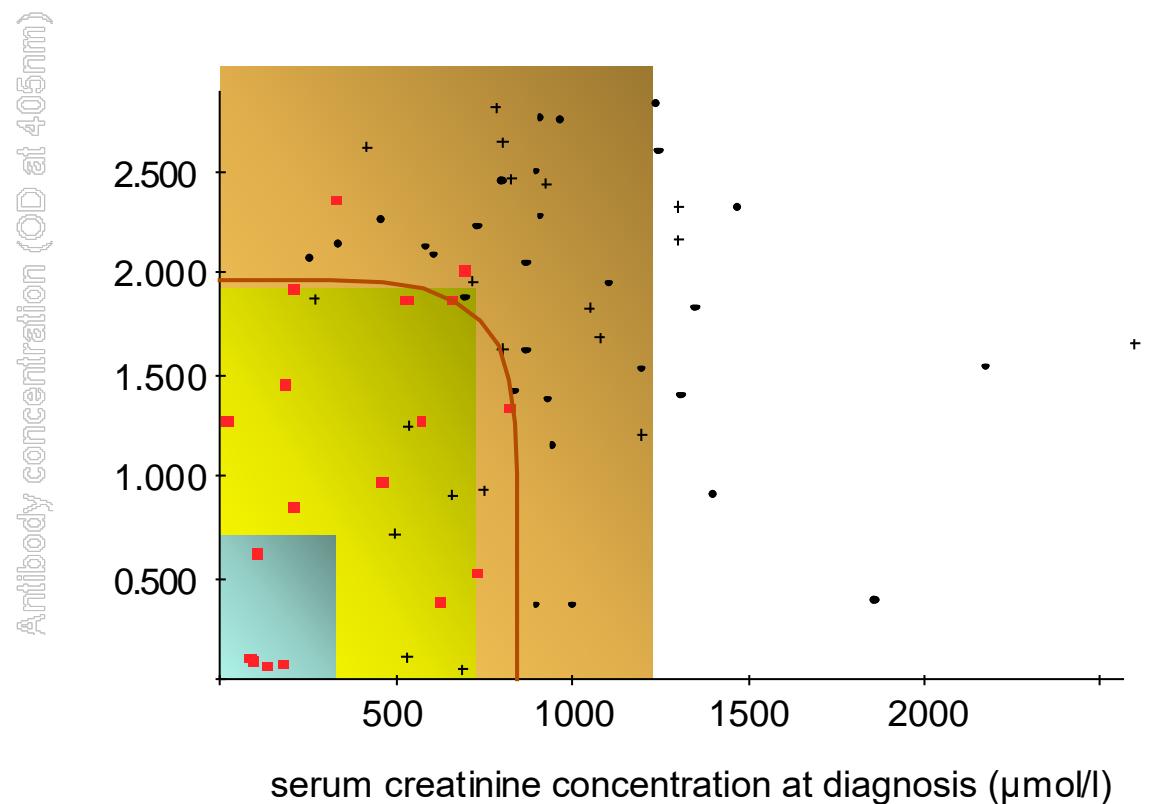
Anti-GBM antibody production



Authors (year)	Country	Period	N	PLEX n (%)	Dead at 6-12 months	Native kidneys at 6-12 months		
						Total	If crea <5-600 at diagnosis	If dialysis/crea >5-600 at diagnosis
Herody et al 1993	France	1984-1992	29	24 (82 %)	2 (7 %)	12 (41 %)	12/13 (92 %)	0/16 (0 %)
Merkel et al 1994	Germany	1982-1992	35	25 (71 %)	4 (11 %)	10 (29 %)	9/14 (64 %)	1/21 (5 %)
Daly et al 1996	Ireland	1976-1991	40	23 (68 %)	3/34 (8 %)	8/34 (24 %)	8/14 (57 %)	0/20 (0 %)
Levy et al 2001	UK	1975-1999	71	71 (100%)	15 (21 %)	29 (41 %)	18/19 (95 %)	11/52 (21 %)
Li et al 2003	Hong-Kong	1992-2003	10	8 (80 %)	2 (20 %)	2 (20 %)	2/6 (33 %)	0/4 (0%)
Segelmark et al 2003	Sweden	1987-1995	75	44 (59 %)	27 (36 %)	16 (21 %)	12/21 (53 %)	4/54 (7%)
Cui et al 2005	China	1997-2002	97	31 (32 %)	na	15 (15 %)	14/28 (50 %)	1/66 (2 %)
Taylor et al 2011	New Zealand	1998-2008	23	17 (74 %)	1(11 %)	11(48%)	na	na
Dammacco et al 2013	Italy	2003-2012	10	10 (100%)	2 (20 %)	6 (60 %)	na	na
Zhang et al 2014	China	2003-2013	28	28 (100 %)	4 (14 %)	8 (29 %)	Na	na
Alchi et al 2015	UK	1991-2011	43	32 (74 %)	5 (12 %)	10 (23 %)	6/8 (75 %)	2/35 (6 %)
MacAdoo et al 2017	UK, Sweden, Czech Rep	2000-2013	78	68/78 (87 %)	11/78 (14 %)	33/78 (42 %)	25/31 (81 %)	8/47 (17 %)
TOTAL			539	75% (402/539)	17% (76/442)	35% (160/454)	76 % (106/140)	9 % (27/311)

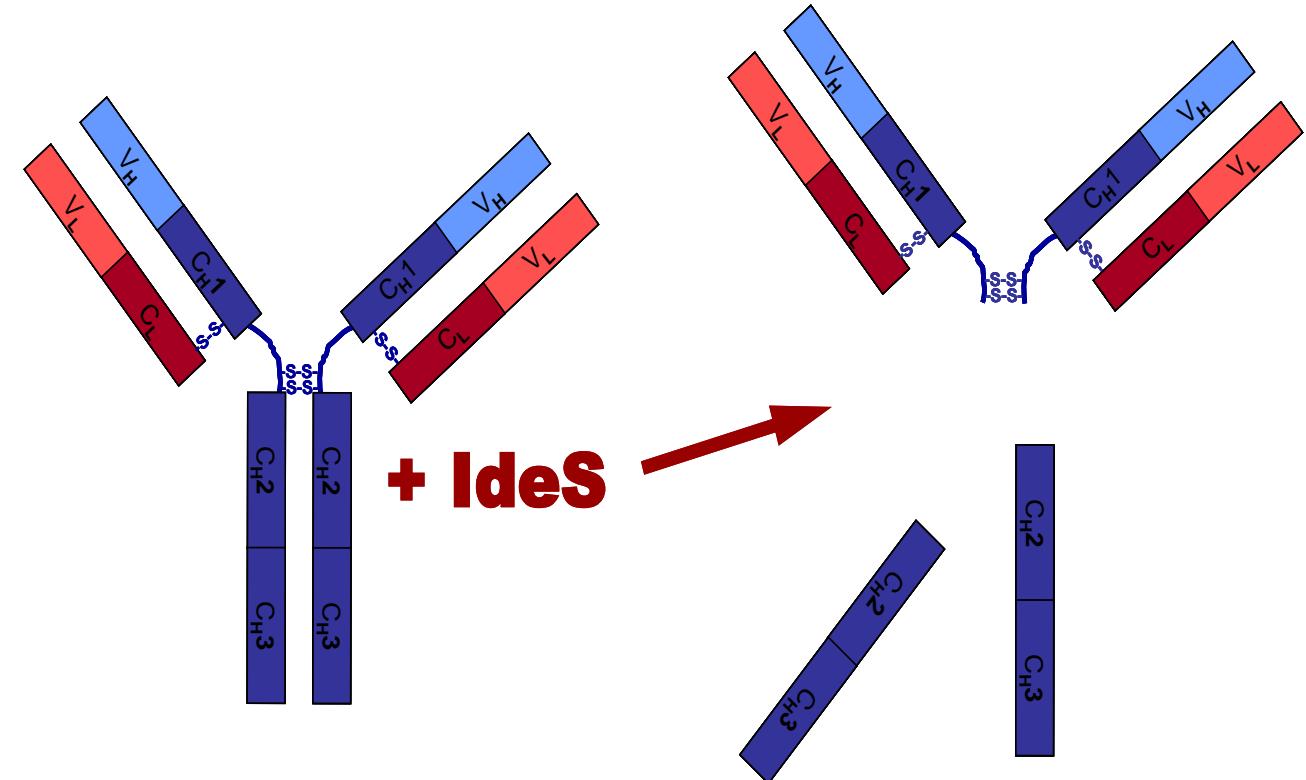
Leves of anti-GBM and prognosis in anti-GBM disease

- Both renal function and antibody levels matter
- In mild cases CYC and steroids is enough
- PLX can save some
- What more can we do?



IdeS = Immunglobulin G degrading enzyme of *Streptococcus pyogenes*

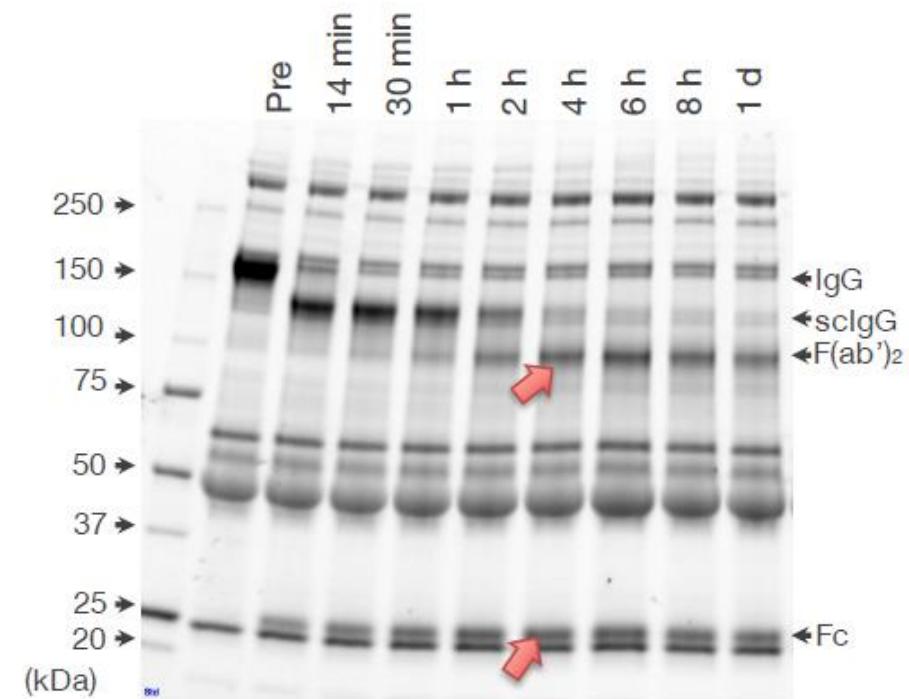
- Made by ordinary *St. pyogenes*
- Discovered by Lars Björck
- Cysteine protease with high selectivity for IgG (vid gly 237)
- Molecular weight 35 kD
- Effective in autoantibody mediated experimental models of ITP¹ and arthritis²
- Official name as pharmacological substance = **imlifidase**



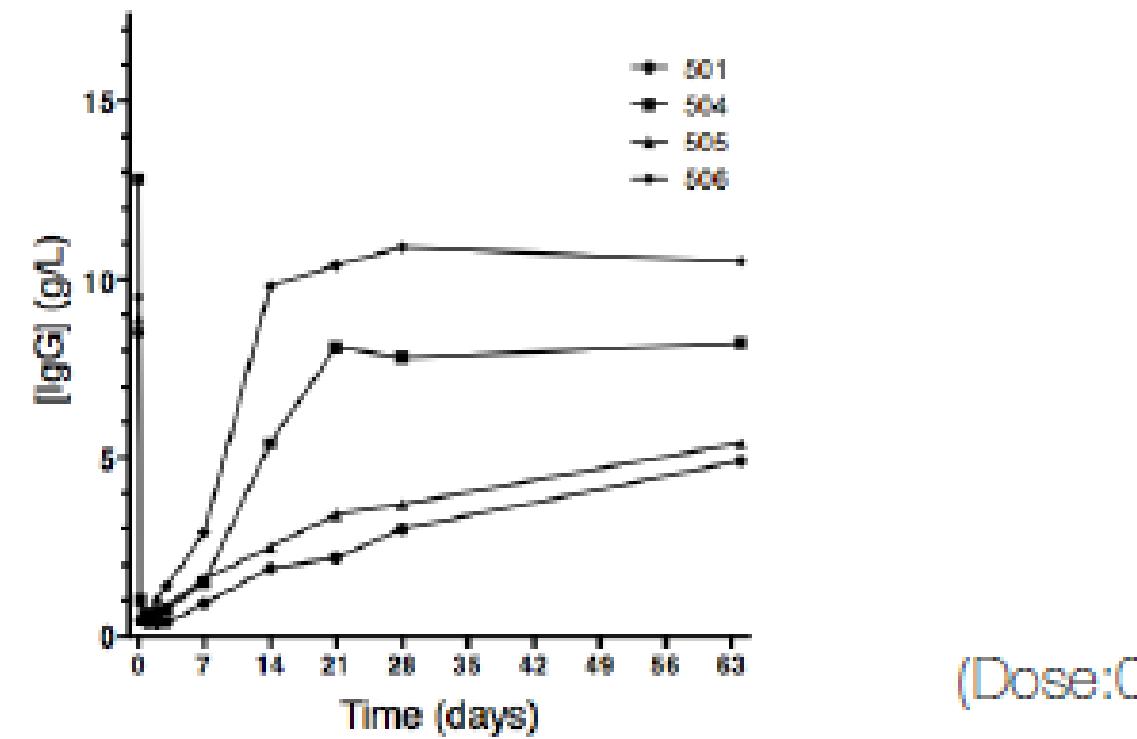
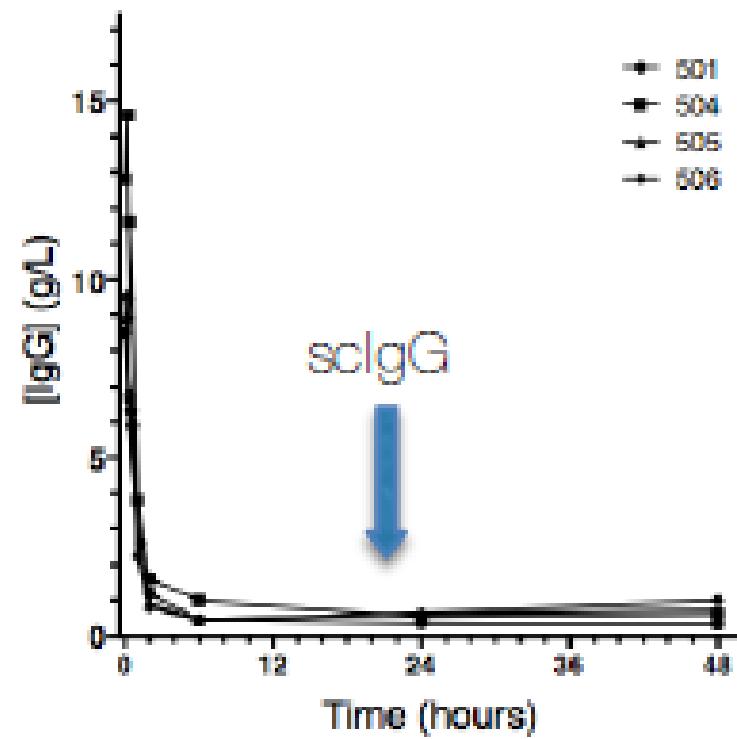
¹Johansson et al, PLoS ONE. 2008;3:1692. ²Nandakumar, Arthritis Rheum. 2007;56:3253-60.

All IgG cleaved within minutes

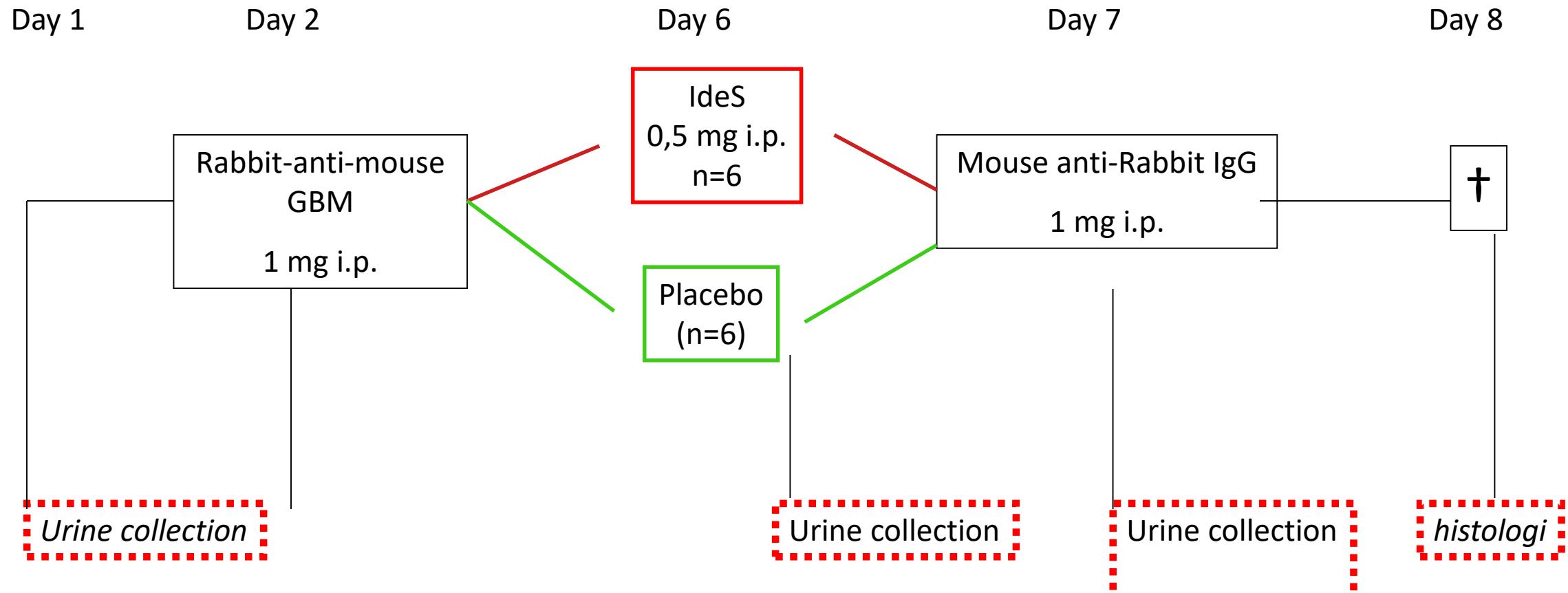
- 0,12 mg/kg iv in 15 min
- All IgG cleaved to scIgG while to dose was given
- Further cleavage to F(ab)2 and two Fc fragments within 4 hours



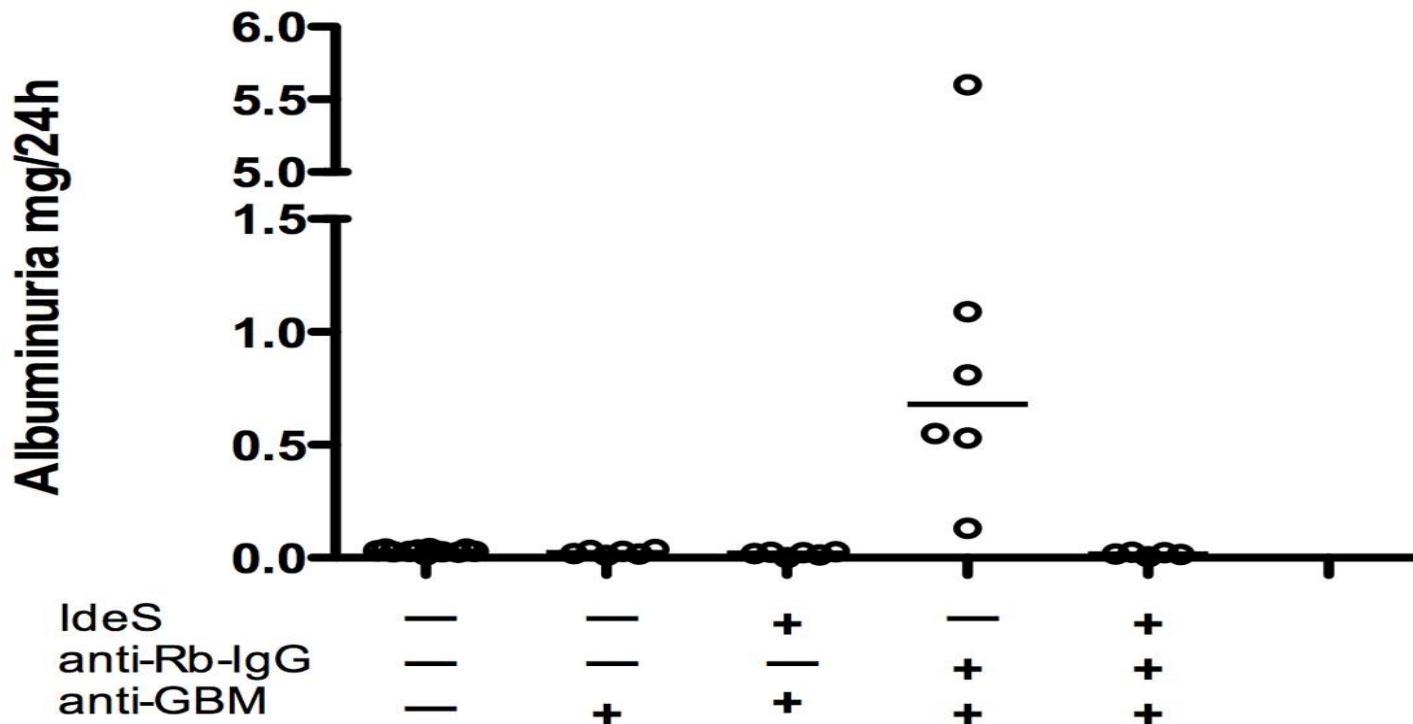
Reappearance of IgG after about a week



Mouse model of anti-GBM disease

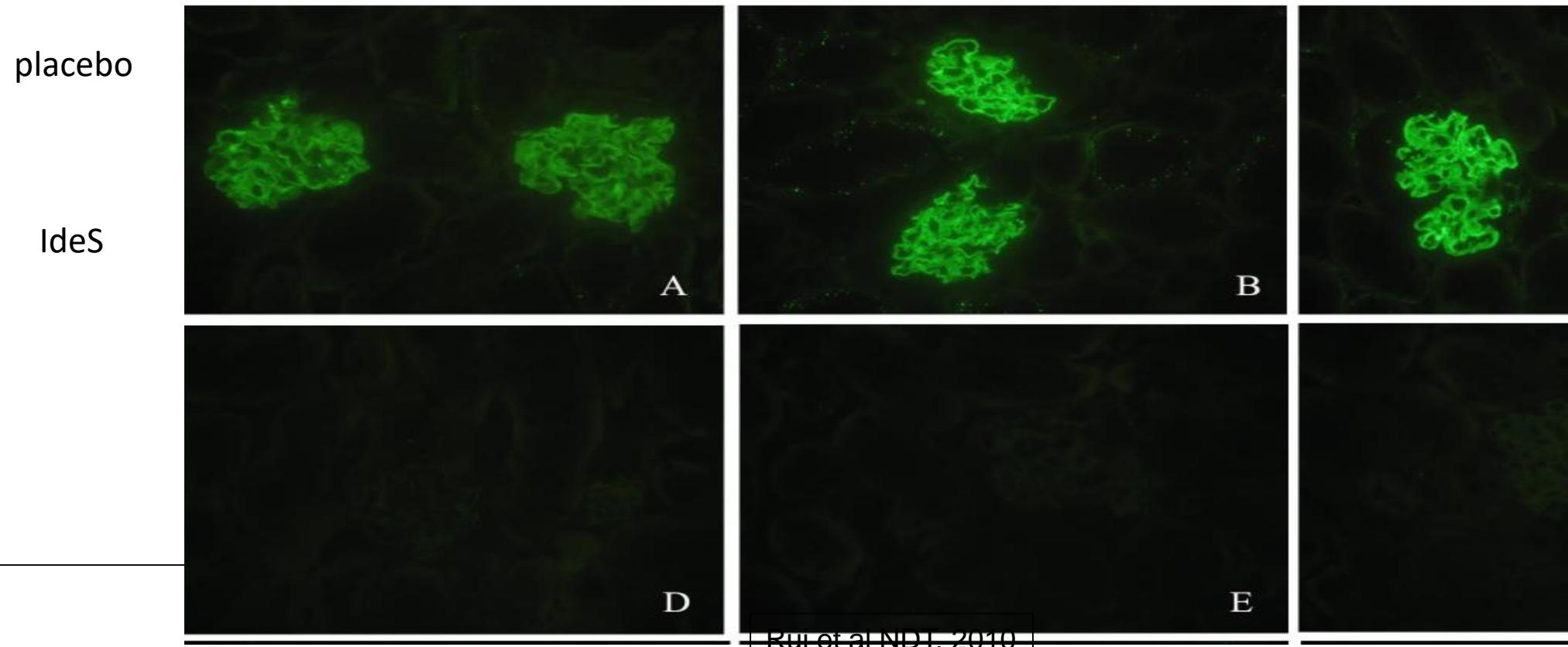


Albuminuria

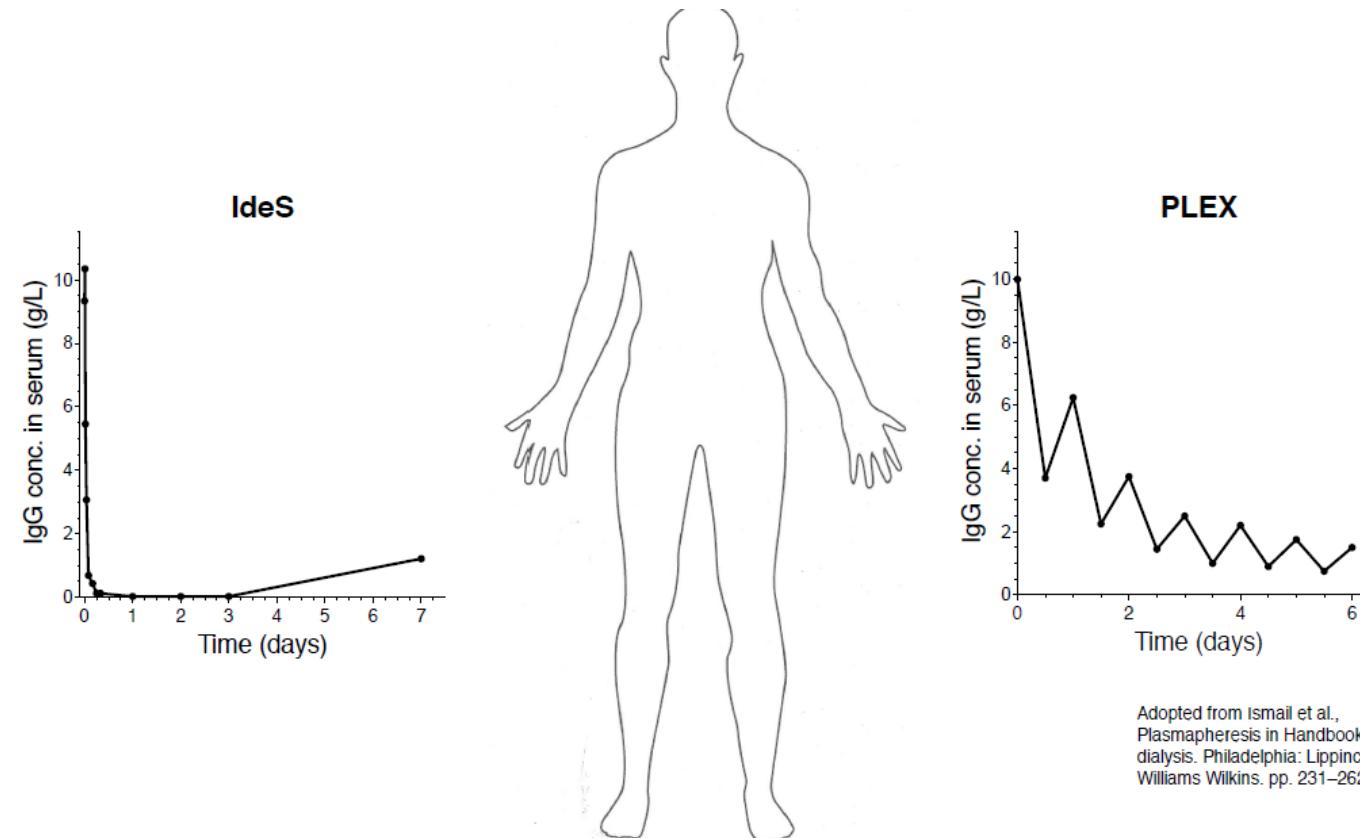


IdeS can cleave IgG bound to mouse kidneys

- Mouse anti-rabbit IgG (Fc spec)



The idea– to treat anti-GBM disease with IdES



Investigator driven study: GOOD-IDES

- Open non-randomized multicenter study
- IdeS on top of standard of care – PLEX on demand
- 15 patients
- 20 sites: 5 in Sweden (Linköping, Uppsala, Lund, Stockholm, Göteborg), 2 in Denmark (Copenhagen, Aarhus), 4 in Austria (Innsbruck, Wien, Feldkirch, Graz) 1 in Czech Republic (Prague), 4 in France (Grenoble, Lille, Paris, Toulouse) and 4 in UK (Cambridge, London (2), Birmingham).
- Total catchment area > 35 million

Inclusion criteria

- Anti-GBM antibodies detected by ELISA above a level that is considered as toxic (indication for PLEX)
- eGFR <15 ml/min/1.73 m² (by MDRD equation) or a drop in eGFR of > 15 ml/min/1.73m² after onset of standard therapy
- Microscopic hematuria and/or active urinary sediment
- >18 years
- Informed consent
- Physically and mentally able to participate

Exclusion criteria

- Anuria for more than 48 hours (less than 200 ml)
- Dialysis dependency for more than 5 days (maximum 3 sessions before signing informed consent)
- Moderate or severe pulmonary hemorrhage. Defined as need for intervention (transfusion, oxygen, assisted ventilation, etc)
- Ongoing infection requiring antibiotic therapy
- History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation.

Compassionate treatment

- 1 patient in Uppsala
 - Failure to induce low anti-GBM titers and refractory disease
- 2 patients in Linköping – dialysis dependent and very high titers.
- Individual license in each case from the Swedish Medicinal Agency
- Drugs from another study

Baseline - compassionate treatment

	Patient 1	Patient 2	Patient 3
Gender	Male	Male	Male
Age	64	75	73
Smoking cessation	3 years ago	27 years ago	2 years ago
Medical history	Type 2 diabetes	Prostatectomy due to cancer, COPD	Hypertension, spinal stenosis, osteoarthritis with knee replacement
First symptoms of anti-GBM disease	Fatigue for 6 weeks	Malaise and macroscopic haematuria for 6 weeks	Malaise for 2-3 months, severe malaise and nausea for 3 weeks, low urinary output
ANCA	negative	negative	MPO-ANCA 28 IE/mL
Urinary output at Ides infusion	500-1000 mL/day	100-300 mL/day	<100 mL/day
Start of dialysis	Day -14	Day -5	Day -6
Pulmonary symptoms	None	Cough tinted with blood	None

Summary

- Double positive ANCA-anti-GBM: worst of both disease
- Membranous-anti-GBM: more proteinuria, better prognosis
- IgG4 anti-GBM: severe pulmonary disease, young smokers, relapses, reactivity to hexamers
- Tregs with specificity for collagen IV α 3 NC1 peptides protects most of us from anti-GBM disease
- IdeS can degrade circulating and kidney bound IgG in minutes

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