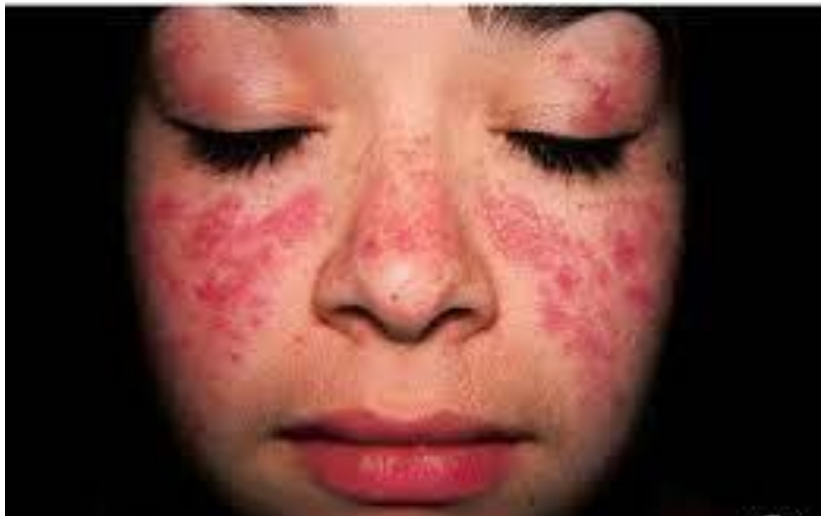
Dr Magnus Nicolson
Invizius Ltd



Measurement	Example
Individual complement plasma proteins	C3, C4, factor B, and other pathway proteins decreased
Total hemolytic complement (snap frozen plasma)	CH_{50} decreased
Individual complement protein metabolism	C3 hypercatabolism
Deposit of complement proteins in tissues	Detection of C3, C4, C1q, C4d, and membrane attack complex (MAC, C5b-9) on glomeruli and skin basement membranes
Plasma activation (split) products	C3dg, iC3b, C4d, MASP-2, C5a, Bb, MAC, and others increased
Cell-bound complement activation products (CB-CAPs)	B cell C4d (BC4d), erythrocyte C4d (EC4d), and platelet-bound C4d (PC4d), among others, increased

The global SLE incidence and newly diagnosed population were estimated to be 5.14 (1.4 to 15.13) per 100 000 person-years and 0.40 million people annually, respectively

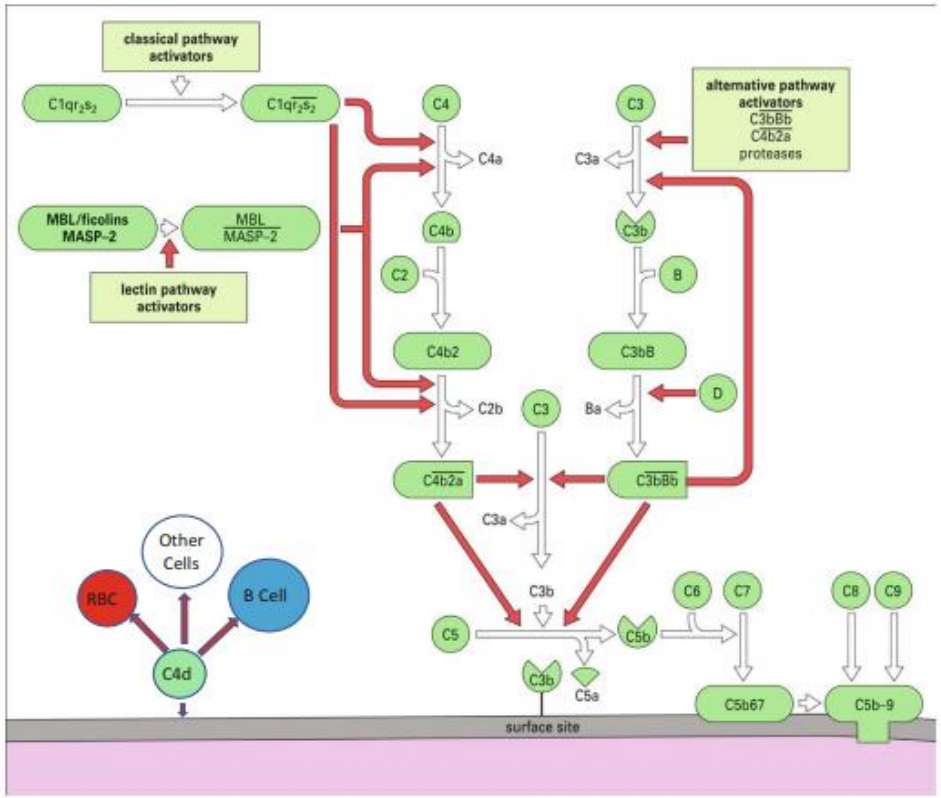
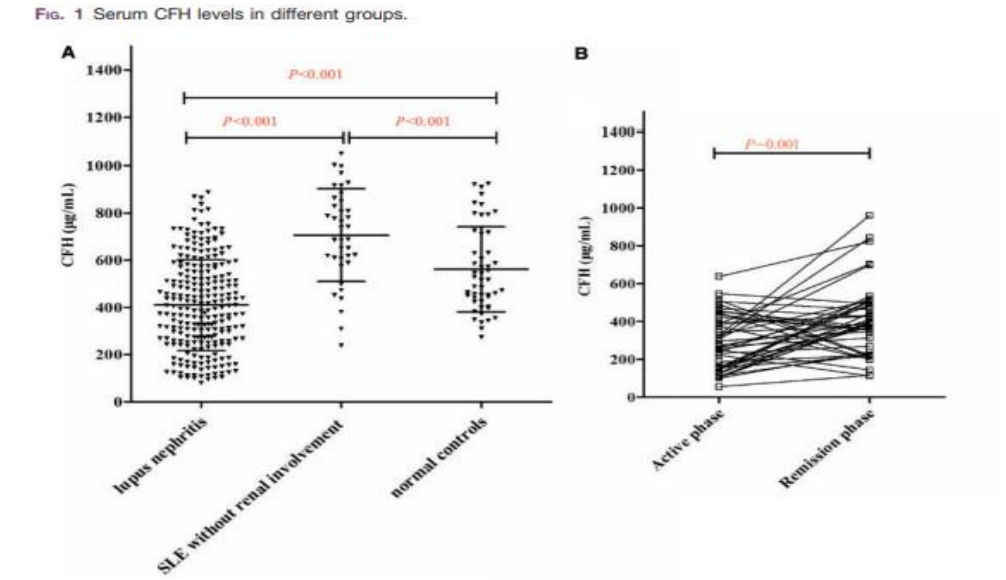


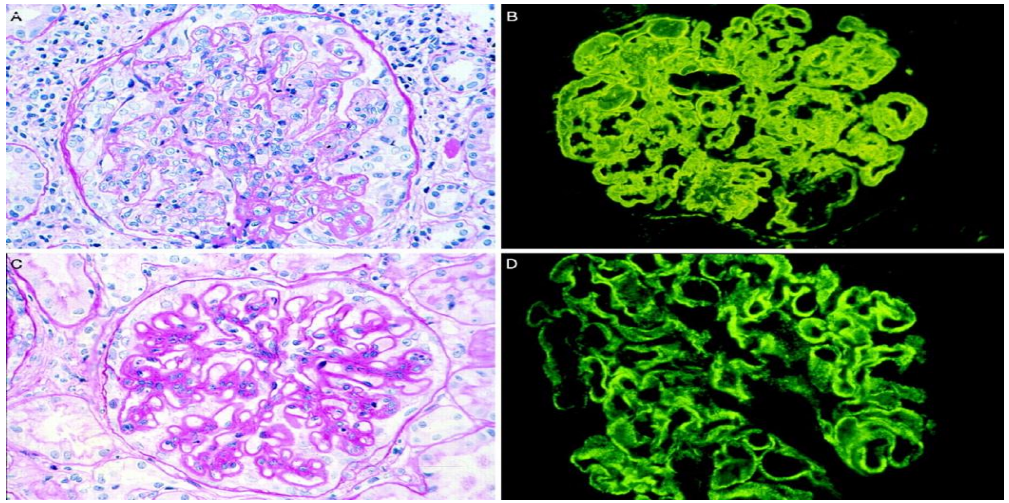
Fig. 1 Pathways of complement activation. Classical pathway activators include surface-bound IgG and IgM and circulating immune complexes. MBL mannose-binding lectin, MASP MBL-associated serine proteinases. Red arrows show feedback (amplification) loops. Modified from Morgan BP: Complement. In: Male D, Brostoff J, Roth DB, Roitt IM, editors. Immunology. 8th edition, Elsevier, 2012

Dr Magnus Nicolson
Invizius Ltd

SLE & Factor H Serum Levels

- The pathogenesis of SLE involves autoantibody production, immune complex deposition, aberrant disposal of apoptosis and complement activation.
- There is strong evidence that activation of the classical complement pathway by immune complexes in SLE is the terminal event leading to tissue damage in many organs.
- Furthermore, there is growing evidence for the and in APS. link between complement activation and thrombosis in SLE
- With complement therapeutics gaining increasing use, it will be important to select those SLE patients who clearly have demonstrable evidence of complement activation and for whom this therapy may be most efficacious.
- Studies suggest that a deficiency in components of the alternative pathway, such as CFH, cause susceptibility to SLE.
- Low serum CFH may be involved in the pathogenesis of SLE, and may be used as a useful biomarker.
- Serum CFH levels might not only reflect LN activity, but may also indicate micro vasculopathy.





Dr Magnus Nicolson
Invizius Ltd

Lupus Nephritis & Factor H

- The presence of anti-C1q antibodies, more prevalent in LN compared to nonrenal SLE, seems to confer an acquired amplification loop of the classical pathway of complement activation.
- Complement activation through both classical and alternate pathways is an important mediator to autoantibody-mediated renal injury.
- A murine model of complement factor H deficiency outlines the importance of the alternate pathway for LN development.
- Complement-targeted therapies have significantly evolved in the past years, with several trials in SLE and LN being currently ongoing.

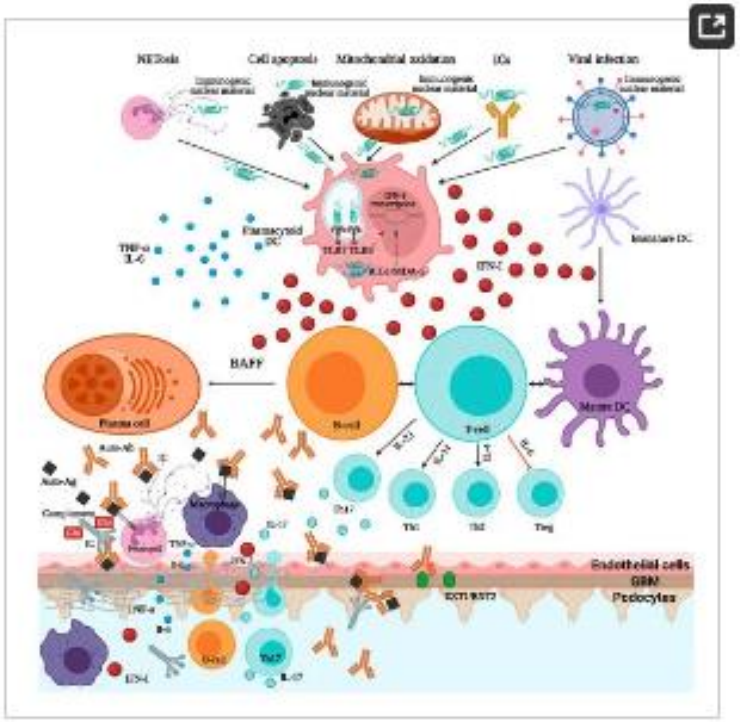


Figure 1. Pathogenesis of lupus nephritis. ICs—immune complexes; TNF—tumor necrosis factor; IL—interleukin; DC—dendritic cell; IFN—interferon; TLR—toll-like receptor; RIG1/MDA-5—retinoic acid inducible gene 1/melanoma differentiation-associated protein 5; BAFF—B-cell activating factor; Ab—antibody; Ag—antigen; Th—T-helper; EXT1/EXT2—exostosin1/exostosin2.

Dr Magnus Nicolson
Invizius Ltd

SLE/LN Investigational Drugs & Mechanisms

Figure 2. Molecular pathways and corresponding therapeutic agents: IFN-I—interferon type I; IFN1-R—type 1 interferon receptor; BAFFR—B-cell activating factor receptor; BCMA—B-cell maturation antigen; TACI—transmembrane activator and calcium-modulator and cyclophilin ligand interactor; CD40L—CD40 ligand; CTLA4—cytotoxic T-lymphocyte antigen 4; CNI—calcineurin inhibitors; TCR—T-cell receptor; MHC—major histocompatibility complex; DC—dendritic cell; BAFF—B-cell activating factor; APRIL—a proliferation-inducing ligand; IL—interleukin; Th—T-helper; APL-2—pegcetacoplan; MASP-2—mannan-binding lectin serine protease 2; C5aR—complement C5aR; IC—immune complex; FcγR—Fc-gamma receptors.

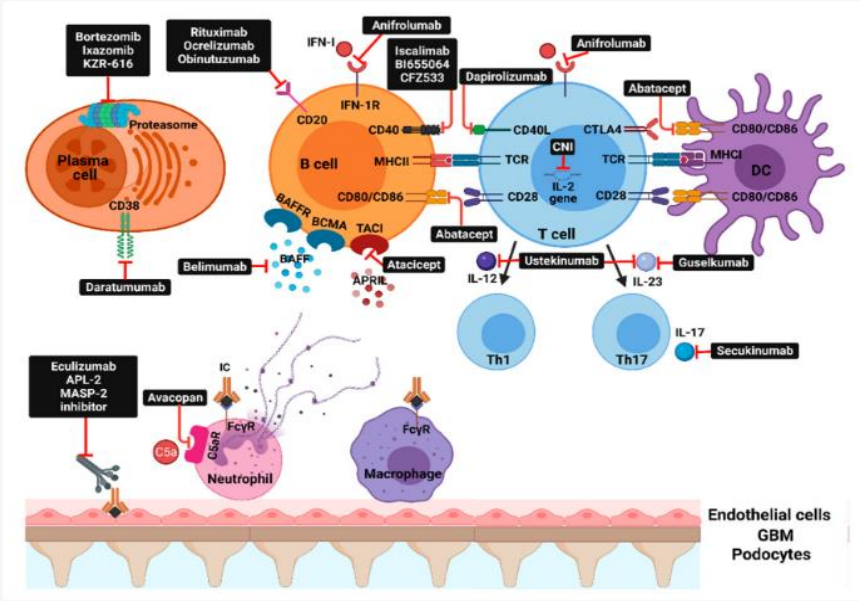


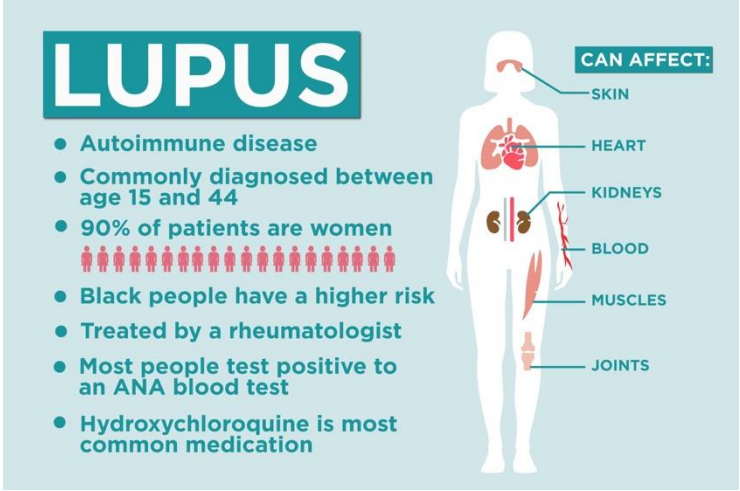
Table 1. Molecular pathways and corresponding agents tested in clinical trials in SLE and LN.

Therapeutic Agent	Molecular Target	Trial Name	Trial Phase	Results	Trial Reference
Anifrolumab	IFN	TULIP-2 TULIP-LN1	III II	Positive Ongoing	[16] NCT02547922
Secukinumab	IL-17A	SELUNE	III	Ongoing	NCT04181762
Ustekinumab	IL-12/IL-23	-	II	Positive	[17,18]
Sirukumab	IL-6	-	II	Endpoint not met	[19]
Guselkumab	IL-23	ORCHID-LN	II	Ongoing	NCT04376827
Dapirolizumab	CD40L	PHOENYCS GO	III	Ongoing	NCT04294667
Iscalimab	CD40	-	II	Ongoing	NCT03610516
BI 655064	CD40	-	II	Ongoing	NCT03385564 NCT02770170
Abatacept	CD28-CD80	ACCESS	III	Endpoint not met	[20]
Atacicept	BAFF/APRIL	-	II/III	Terminated early due to unanticipated safety issues	[21]
Voclosporin	Calcineurin	AURA AURORA	II III	Positive Positive (results to be published)	[22] NCT03021499
Belimumab	BAFF	BLISS-LN CALIBRATE	III II	Positive Endpoint not met	[23] [24]
Blisibimod	BAFF	CHABLIS7.5 CHABLIS-SC2	III III	Withdrawn Withdrawn	NCT02514967 NCT02074020
Rituximab	CD20	LUNAR	III	Endpoint not met	[25]
Ocrelizumab	CD20	-	III	Stopped early due to higher number of serious infections with ocrelizumab	[26]
Obinutuzumab	CD20	NOBILITY REGENCY	II III	Positive (results to be published) Ongoing	[10] NCT04221477
Daratumumab	CD38	-	-	Therapy for consideration	[27]
Ianalumab	BAFF receptor B-cells	-	-	Therapy for consideration	-
Bortezomib	Plasma cell	-	IV	Withdrawn	NCT01169857
Ixazomib	Plasma cell	-	I	Insufficient enrolment	NCT02176486
Eculizumab	C5	-	-	Therapy for consideration	[28]
Ravulizumab	C5	-	II	Ongoing	NCT04564339
Avacopan	C5a	-	-	Therapy for consideration	-
Narsoplimab	MASP-2	-	II	Ongoing	NCT02682407
APL-2	C5	-	II	Ongoing	NCT03453619
LNP023	Factor B	-	II	Therapy for consideration	-

Dr Magnus Nicolson
Invizius Ltd

Lupus Nephritis Market Opportunity for H-Guard® Platform

- The global market for lupus drugs (systemic lupus erythematosus and lupus nephritis) to reach **$3.1 billion by 2027**, growing at **CAGR 8.4%** over the forecast period, driven by increasing prevalence of disease, uptake of biologics, and improvements in disease awareness and diagnosis.
- The Lupus Foundation of America estimates that 1.5 million Americans, and at **least five million people worldwide,** have a form of lupus.
- Lupus nephritis is the **leading cause of morbidity** and mortality in SLE, developing in 50% to75% of Asian SLE patients



- There is a clear rationale for modulation of the complement system as a therapeutic approach for the treatment of LN.
- The optimal therapeutic will spare the early components of the classical and lectin pathways, in favour of inhibiting the alternative and terminal pathways, thereby blocking the effects of the pro-inflammatory complement split products, preventing activation of the MAC, or enhancing the intrinsic complement regulatory pathways to the level needed to meet the increases that occur in complement activation.
- A variety of novel small molecules and biologics have been developed that meet these criteria, and clinical trials are, or shortly will be, underway to test their efficacy.
- The pre-clinical and clinical data suggest that a complement-targeted approach such as H-Guard® should be successful in LN.

Dr Magnus Nicolson
Invizius Ltd

INVIZIUS