NavigAID™ SLE

Harnessing the utility of auto antibodies to overcome challenges associated with clinical development in Systemic Lupus Erythematosus (SLE).

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Oncimmune®

At a glance

NavigAID SLE is a patient stratification array that separates and defines subtypes in Systemic Lupus Erythematosus (SLE), overcoming issues of heterogeneity in disease classification and enabling new approaches to successful drug development.

Fundamental to the ImmunoINSIGHTS NavigAID approach is the SeroTag™ process, a proprietary biomarker discovery engine that helps in understanding the molecular basis of complex autoimmune diseases. Using this diagnostic 'magnifying glass' Oncimmune has developed **NavigAID SLE**, a well-defined antigen panel that delineates disease subtypes and increases the probability of successful SLE therapy.

SLE is an autoimmune disease with a wide range of clinical manifestations. It affects approximately 5 million people worldwide (1) and its prevalence varies in different geographies (2). SLE accounts for around 70% of all cases of lupus, other forms being cutaneous lupus, drug-induced lupus and neonatal lupus (3). In around 50% of people living with SLE, a major organ or tissue, such as heart, lungs, kidneys or brain, will be affected.

Recent clinical developments in SLE, and the associated lupus nephritis, have focused on inhibiting the activation of autoreactive B-cells or pathways leading to autoimmunity and inflammation. Currently, Benlysta® (Belumimab, GSK) is the only targeted therapy to have received regulatory approval, although Rituxan® (Roche) is also used as an off-label treatment (4)

Development of SLE treatments lags far behind those for rheumatoid arthritis (RA) and other autoimmune diseases. A primary issue in SLE drug development is defining the right patient population for a trial. However, there are many factors which hamper SLE drug development (5). These include:

- Pathogenesis of SLE is multi-factorial and includes genetic, environmental, and hormonal factors;
- SLE is an extremely complex disease that affects multiple organs and is described by highly variable clinical profiles;
- There are differences in disease prevalence, activity and clinical manifestations among different ethnic groups;
- The remitting and relapsing nature of the disease means that those treated with placebos can show significant response rates (6);
- In clinical trials it is a challenge to apply composite responder indices to the variable clinical presentations.

For people living with SLE, the various symptoms and laboratory abnormalities can occur in different combinations at different times. As a result, studies of SLE may use several, potentially conflicting, definitions of the disease (7). Solving the problem of SLE patient heterogeneity is therefore pivotal for the clinical development of effective and curative therapies.

Significant progress has been made in understanding molecular disease mechanisms, however, there remains an unmet need for novel diagnostic biomarkers and assays that enable precise disease characterisation, patient stratification and response prediction.

The ImmunoINSIGHTS **NavigAID SLE** array meets this need exactly and is set to become an indispensable part of any SLE clinical development programme.

SLE pathogenesis and therapeutic targets

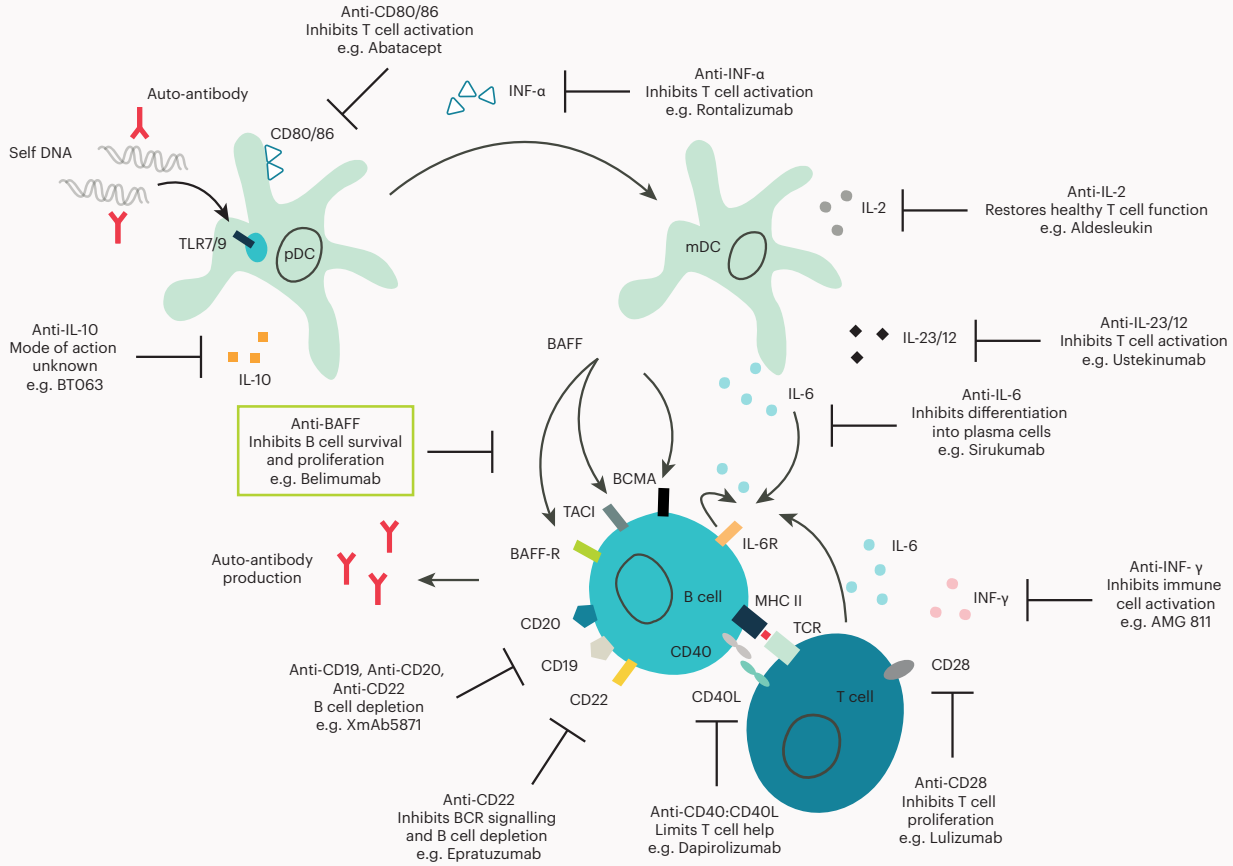
SLE is an autoimmune disease affecting approximately 5 million people worldwide with a wide range of clinical manifestations. Standard treatment options tend to rely on non-specific immunosuppression and there is a significant medical need for new, more focused therapies. However, the US Food & Drug Administration (FDA) has given approval to only one new treatment for SLE in 50 years: Benlysta®, which was approved in 2011 for use in both adults and children with SLE.

As understanding of SLE continues to improve, more targeted approaches to drug treatment are emerging. Current developments focus on key modulators of chronic inflammatory and immunological processes with various therapies in clinical trials. B-cells play a central role in SLE pathogenesis through a combination of antibody-independent and antibody-mediated actions, including presentation of autoantigens to T-cells. This autoimmune reaction can induce tissue damage and the release of type I interferon (IFNI) by dendritic cells (Figure 1) (8, 9), which can influence the development and progression of SLE.

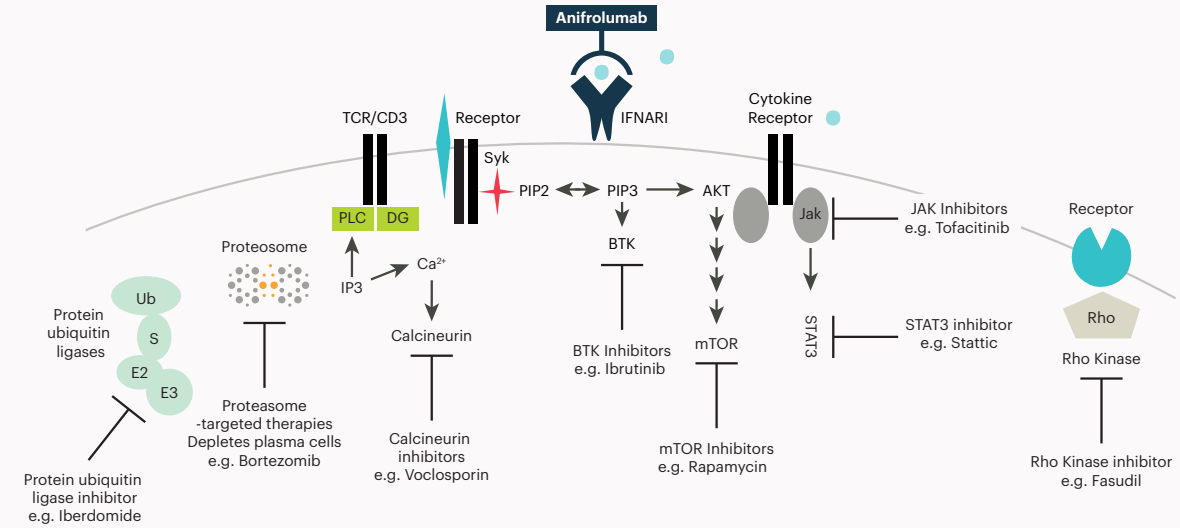
Recent clinical developments in SLE have focused on inhibiting the activation of autoreactive B-cells by targeting cytokines and B-cell-specific surface receptors involved in B-cell differentiation and maturation, thereby reducing autoantibody production. Drugs representing different therapeutic strategies have now reached the later stages of clinical trials and include: cytokine infusions, antibodies against cytokines, and small molecule kinase and phosphatase inhibitors (10).

Figure 1: Overview of the multi-targeted approaches for the treatment of SLE (9, 10)

a) External pathways



b) Intercellular pathways



The need for biomarkers in the clinical development of SLE therapeutics

With the exception of Benlysta®, approval for novel SLE medicines lags behind that for other autoimmune diseases such as rheumatoid arthritis (RA). An analysis, performed in 2018, of pipeline products that failed to gain approval indicated that these therapies demonstrated efficacy and safety in earlier-phase trials, but this was not replicated in larger late-phase trials (5).

It is likely that several challenges are impeding drug development for SLE (11) and one of the most critical and pressing priorities is to enrol homogeneous patient groups in clinical trials (12). These patient groups are difficult to enrol because:

- The pathogenesis of SLE is multi-factorial, including genetic, environmental, and hormonal factors, and the exact cause of SLE remains unclear;
- SLE is a complex disease that affects multiple organs and is described by extremely variable clinical profiles. This variability in disease presentation suggests that SLE is a heterogeneous group of diseases (and thus a syndrome) which can be divided into smaller more homogeneous subtypes, each having different baseline biomarker patterns and disease characteristics;
- As a result of its variable clinical presentation, misclassification of SLE remains an issue, in particular when applying the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (13, 14);
- Differences among ethnic groups can be found in: disease prevalence, disease activity, clinical manifestations, autoantibody serology and efficacy of treatments (15);
- Due to the remitting and relapsing nature of the disease and the high standard of care, treated placebo groups show significant response rates. These compromise the outcome of clinical trials (11);
- The variable clinical presentation creates a challenge in uniformly applying complex composite responder indices in large clinical trials. Furthermore, different disease activity indices – i.e. the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG) - may yield different drug and placebo response rates (11).

The heterogeneity of SLE patients represents an enormous challenge for the clinical development of effective and curative therapies. The ability to define true SLE patients, and to dissect SLE into different subtypes with specific patterns of biomarkers and organ involvement, is especially important for evaluating therapeutic efficacy in clinical trials (11, 16)

Ideally, when recruiting for clinical trials, patients should be characterised not only by standard anti-nuclear antibody (ANA) testing, but by high autoantibody levels to characteristic SLE-specific antigens. Not only can the application of biomarkers and autoantibodies support the enrolment of homogeneous patient groups they can also be used to monitor how well patients have been recruited at different study sites.

Although significant progress has been made in understanding molecular disease mechanisms, there is still an unmet need for novel diagnostic biomarkers and assays for precise disease characterisation, patient stratification and response prediction (17).

NavigAID SLE

The ImmunoINSIGHTS SLE stratification panel

NavigAID SLE is based on analysis from a robust database of more than 1,000 SLE patients (>1,300 serum samples) and provides answers to the following questions:

1. *Can we ensure enrolment of an **appropriate SLE patient population?***

   YES. According to the literature, up to 20% of SLE patients are misdiagnosed (Narain, Richards et al. 2004). Additionally, and in order to characterise cross-reactivity, we also include diagnostic antigens from other autoimmune diseases.

2. *Can we identify patients with **high disease activity** and/or an SLE specific **type I Interferon inducible signature?***

   YES. Patients with high disease activity are characterised by an extended repertoire of autoantibodies (Villarreal, Drenkard et al. 1997). Such patients are further distinguished by activation of the interferon-I pathway and a characteristic pattern of autoantibodies, which target IFN-inducible genes. The levels of anti-dsDNA and anti-C1q antibodies are associated with lupus nephritis and increases in their titre, which precede flare-ups of disease activity.

   Studies also note that patients with SLE and those with Sjogren's syndrome demonstrated an excess of autoantibodies against interferons and the interferon-responsive chemokine interferon-inducible protein 10 (IP-10) (18).'

   Cytokine dysregulation is characteristic of SLE and offers the potential for identifying patient subsets before the onset of clinical disease and during established disease (19). With the advent of increasing numbers of therapeutic anti-cytokine antibodies, defining the role of endogenous anti-cytokine autoantibodies may help in identifying suitable patient subsets more likely to respond.

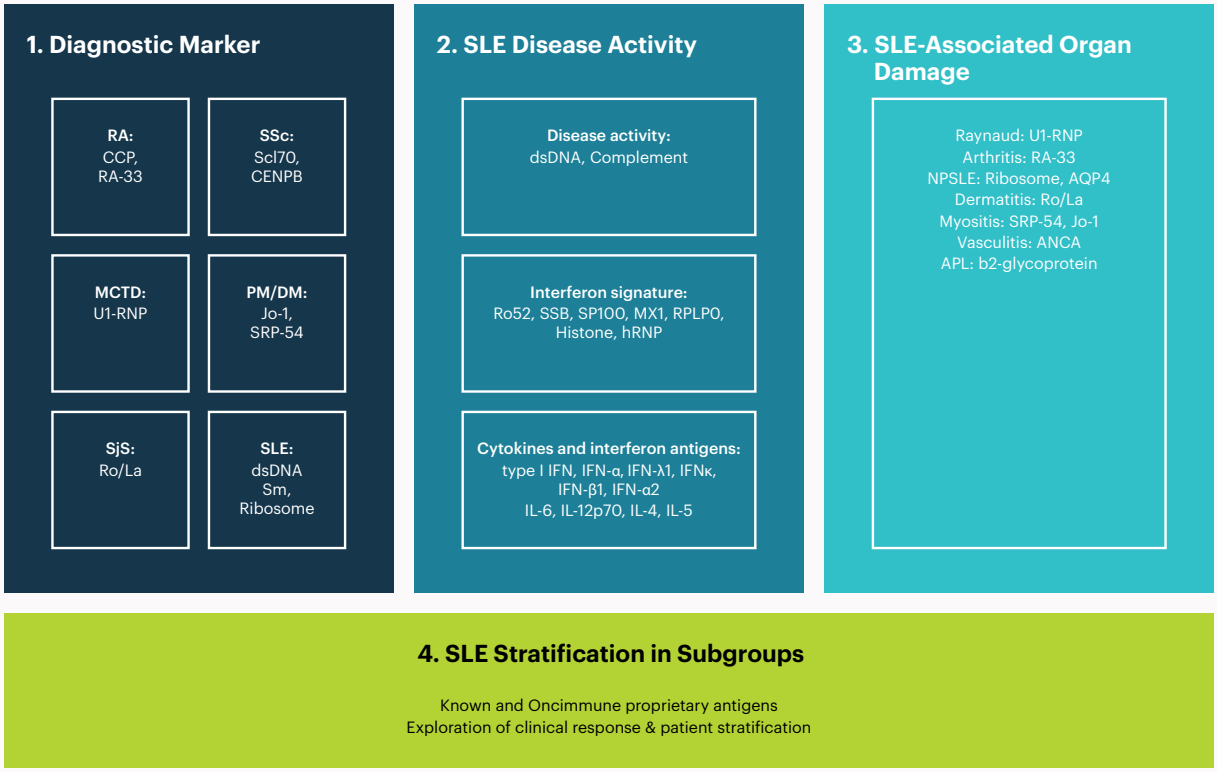
3. *Can we diagnose/predict SLE associated **organ damage**?*

   YES. Certain autoantibodies seem to be associated with specific organs. For example, high titres of anti-dsDNA antibodies are associated with lupus nephritis, whereas anti-U1-RNP autoantibodies are associated with Raynaud's phenomenon and a lower chance of nephritis.

4. *Is it possible to stratify SLE into **different subtypes**?*

   YES. The ImmunoINSIGHTS NavigAID SLE combines selected known and proprietary biomarkers, enabling the characterization of distinct SLE subtypes.

Figure 2: ImmunoINSIGHTS NavigAID SLE



Technical aspects of the NavigAID SLE

SeroTag®, a technology developed by Oncimmune, utilises the bead-based Luminex® technology platform for autoantibody measurements. Luminex is an FDA-approved technology that offers a number of advantages over single analyte technologies:

- Scalability with regard to multiplexing
- Low sample requirement (max. 50 µL)
- No platform change required for CDx development

NavigAID SLE array comprises a total of 96 autoantigens and includes 4 controls in order to provide answers to the four questions detailed above; 47 of these antigens are known antigens that are used as *in vitro* diagnostics (IVDs) and are included in Table 1, and 40 are novel, proprietary Oncimmune antigens.

The Luminex platform provides quantitative autoantibody data, enabling comparison of autoantibody levels in patients, along with the analysis of a reduction in autoantibody levels during treatment.

Autoantibody-based SLE patient stratification

The remitting/flaring nature of SLE is associated with statistically problematic high placebo response rates. Consequently, demonstrating superior efficacy over a placebo, and predicting response to treatment, is crucial for efficient clinical development and regulatory approval.

This challenge underscores the need for technologies and biomarkers that allow definition of more homogeneous subtypes of SLE patients that are more likely to respond to new treatments.

NavigAID SLE has been specifically developed to address the critical challenges in the clinical development of novel drugs for SLE via the simple measurement of serum biomarkers.

As such, it enables specific differential diagnosis, state-of-the-art disease activity assessment and IFN-1 signature comparison, together with a disease stratification approach that will benefit any new SLE treatment. Furthermore, it has the potential to provide the basis for companion diagnostics (CDx).

Further insight to NavigAID SLE

Ensuring enrolment of an appropriate SLE patient population

According to the literature, up to 20% of SLE patients are misdiagnosed (20). SLE is regarded as an autoantibody-mediated disease, and positive autoantibody tests have become a requirement for recruiting patients into clinical trials. However, the ANA test is not specific for SLE because anti-nuclear autoantibodies occur in other rheumatic diseases, infectious diseases and up to 20% of the general population (21, 22). Thus, despite high sensitivity for SLE, the ANA assay lacks specificity and is associated with a risk of over- or misdiagnosing SLE (20, 23).

In contrast to ANA, anti-dsDNA tests are more specific for SLE, but less sensitive (30–70%) and correlate with disease activity in lupus, specifically nephritis (24). Thus, to ensure that there is a consistent inclusion of SLE patients into clinical trials, a positive ANA test should be re-evaluated by subsequently analysing different nuclear antigen targets.

In order to characterise patients who are not exhibiting unambiguous SLE but who have overlapping features with other rheumatic/ autoimmune disorders, we also include diagnostic antigens across this spectrum. For example, the anti-cyclic citrullinated peptide (CCP) antibody is an established marker in the diagnosis of RA but is also infrequently found in SLE where it serves as a useful marker of erosive arthritis (25).

To define a homogenous group of specific SLE therapy responders, antibody reactivity towards diagnostic SLE and autoimmune antigens needs to be analysed.

Identifying patients with high disease activity and/or an SLE specific type I interferon (IFN) inducible signature

DNA-containing immune complexes can activate dendritic cells to produce type I IFN (Figure 1). In conjunction with the activation of gene expression profiles for pro inflammatory cytokines, IFN-α also enhances the expression of a subset of autoantibody targets such as Ro52 or ribosomal P proteins (Table 1).

Specific clinical features, including lupus nephritis and more severe disease, are associated with the high expression of IFN-induced genes and specific autoantibody patterns, including autoantibodies against Ro, U1-RNP, Sm and dsDNA, found to be associated with a high type I IFN score (26). The type I IFN signature in blood has been used as a pharmacodynamic marker during the clinical development of anti-IFN-alpha therapies. As such, an SLE-specific PCR-based type I IFN signature is often used in clinical trials.

Oncimmune provides a serum-based approach to characterise a clinically meaningful group of SLE patients with autoantibodies against type-I-Interferon pathway proteins and high disease activity.

Diagnosis/prediction of SLE associated organ damage

The autoantibody profile helps to predict SLE subsets with typical organ manifestations. High titres of anti-dsDNA antibodies are associated with lupus nephritis, whereas anti-U1-RNP autoantibodies are associated with Raynaud's phenomenon and a reduced probability of nephritis. Combined anti-Ro/La antibodies are associated with secondary Sjögren's syndrome (SjS) and photosensitivity but are absent in lupus nephritis. Moreover, anti-ribosomal P antibodies are clearly associated with CNS lupus (Table 1; (24)).

NavigAID SLE analyses markers with the potential to predict and define patients with specific organ involvement and allows for a specific analysis of such patient groups.

Stratification of SLE into different subtypes

In SLE, B-cells produce autoantibodies associated with distinct clinical subtypes (Table 1). A typical feature of SLE is the accumulation of autoantibody reactivities and intra- and inter-epitope spreading over time. Furthermore, the co-occurrence of autoantibodies in SLE patients has rarely been analysed.

Previous studies indicate that subspecies of autoantibodies to Ro/SSA and La/SSB are present in 25–50% of SLE patients and levels of these autoantibodies are associated with the MHC class II gene locus (HLA-DRB1*03:01) (Harley, Sestak et al. 1989; Morris, Fernando et al. 2014). Thus, based on the HLA haplotype and associated autoantibody pattern, SLE can already be dissected into two subsets of Ro/La and Sm/RNP-positive subtypes (27).

Oncimmune has developed a set of known and proprietary markers to stratify SLE into additional subtypes to help provide a more detailed picture of this multifaceted disease.

Oncimmune analysed over 1,300 SLE samples with different disease states and ethnicities and a comprehensive portfolio of SLE-specific autoantibody signatures were discovered. Based on a set of 64 autoantigens, we have analysed "linked sets" of autoantibody reactivities and used these linked reactivities to identify SLE patients with a homogeneous autoantibody profile.

Figure 3 shows a contingency heatmap of SLE patients in which the number of positive autoantibodies per SLE patient is colour coded, green (low) to red (high), with up to 64 autoantibodies per patient. This enables the identification of distinct patient subtypes/clusters sharing the following characteristics:

Patient Subgroup C1

This is a highly reactive patient group, with positive autoantibody reactivity towards a large number of autoantigens. Patients in this cluster share the presence of a high number of more than 10 markers. However, this cluster segregates into two further subtypes with reactivity towards partially unique markers. Reactivity towards an expanded set of autoantibodies correlates with high disease activity and upregulated expression of IFN-responsive genes (28).

Interestingly, a previous study for SLE patients treated with Rituximab demonstrated that patients with an expanded baseline repertoire of anti-nuclear autoantibodies had a shorter clinical response to B-cell depletion therapy (29).

Patient Subgroup C2

This subgroup is characterised by a similar number of reactive autoantigens (>15 markers), but individual patients share only a smaller fraction of markers with each other. Hence, this subgroup is highly reactive, but more heterogeneous.

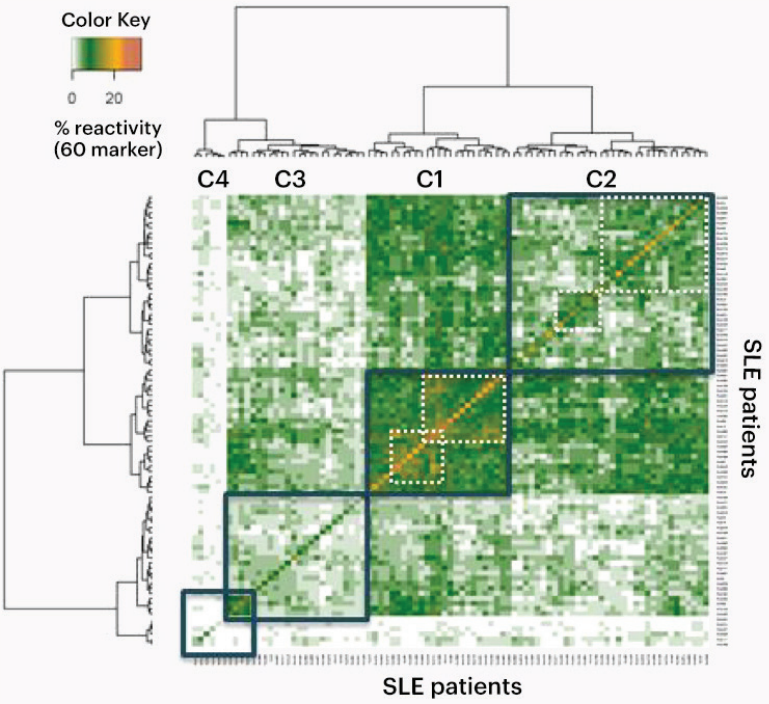
Patient Subgroup C3

The third patient subgroup typically includes patients with reactivity against a small number of autoantibodies (5–10 markers) and a low degree of shared reactivities.

Patient Subgroup C4

The fourth subgroup includes a small number of patients who can be defined as outliers in terms of autoantibody reactivity. This group of patients can be characterised by very low reactivity and a low degree of similarity to other patients. In the context of clinical studies, these patients need further characterisation as they might be misclassified as SLE.

Figure 3: Patient clustering based on shared autoantibody reactivity



Conclusion

NavigAID SLE measures autoantibody markers linked to the SLE disease pathology and clinical manifestations. Based on linked sets of autoantibody markers it is now possible to define at least four disease subtypes in SLE patients. These patient groups are characterised by the co-appearance of autoantibody markers and the total number of shared autoantibody markers.

For the first time, this approach allows us to define more homogeneous patient groups and to overcome the serological and clinical heterogeneity of SLE. Oncimmune has specifically developed this array to prospectively address the critical challenges in the clinical development of novel drugs for SLE with the simple measurement of serum biomarkers.

NavigAID SLE can contribute to the definition of a homogeneous group of potential SLE therapy responders. This screening tool therefore has the ability to help address the unmet need for specific biomarkers that allow for precise disease diagnosis, patient stratification and response prediction, and should become part of any SLE clinical development programme.

Appendices

Table 1: Autoantibody markers used in different clinical settings of SLE

		Diagnostic Antigens											Organ/Tissue Manifestations									
Autoantibodies	**Antigen**	SLE	MCTD	SjS	SSc	PM/DM	pAPS	RA	ANCA-Vasculitis	Drug-vasculitis	PBC	NMO	Nephritis	Vasculitis	Myositis	Arthritis	Raynaud	NPSLE	Dermatitis	Hematology	Disease Activity	
dsDNA	dsDNA																					1
Sm-Antigen	Sm-B/B' (SNRPB)																					1
Sm-Antigen	SmD1 (SNRPD1)																					
Sm-Antigen	SmD3 (SNRPD3)																					1
U1-snRNP	U1-snRNP 70 (SNRNP70)																					1
U1-snRNP	U1-snRNP A (SNRPA)																					1
U1-snRNP	U1-snRNP C (SNRPC)																					1
Ribosomal P	RPLP1																					1
Ribosomal P	RPLP0																					1
Ribosomal P	RPLP2																					1
Complement	C3																					1
SS-A	Ro52 (TRIM21)																					2
SS-A	Ro60 (TROVE2)																					2
SS-B / La	SSB																					2
SCl-70	TOP1																					3
Centromere	CENPA																					3
Centromere	CENPB																					3
Centromere	CENPC																					3
PM/Scl	EXOSC10																					3
anti-citrullinated antigen	ACPA																					4
tRNA-Synthetase	Jo-1 (HARS)																					5
SRP	SRP54																					5
tRNA-Synthetase	PL-7 (TARS)																					5
tRNA-Synthetase	PL-12 (AARS)																					5
tRNA-Synthetase	EJ (GARS)																					5
tRNA-Synthetase	KARS																					5
TIF1-g	TRIM33																					
Mi-2	CHD3																					6
Mi-4	CHD3																					
MDA5	IFIH1																					
M2-Antigen	OGDC-E2 (DLST)																					6
M2-Antigen	BCOADC-E2 (DBT)																					6
M2-Antigen	PDC-E2 (DLAT)																					6
SP100	SP100																					6
p-ANCA	Lactoferrin (LT)																					7
p-ANCA	Elastase (ELANE)																					7
p-ANCA	Cathepsin G (CTSG)																					7
p-ANCA	Alpha-enolase (ENO1)																					7
p-ANCA	Lysozyme (LYZ)																					7
c-ANCA	Myeloperoxidase (MPO)																					7
c-ANCA	Proteinase 3 (PRTN3)																					7
Histone	H2a																					7
Histone	H2b																					7
Histone	H4																					7
Aquaporin-4	AQP4																					8
ß2-Glykoprotein I	APOH																					8
RA-33	hnRNP (HRNPA2B1)																					4
Ku	Ku80 (XRCC6)																					5
Ku	Ku70 (XRCC5)																					5

Left side of table: antigens used for diagnosis of SLE, and differential diagnosis of other rheumatic diseases: **Red:** main diagnostic AAB; **dark grey:** frequently associated with disease; **light grey:** associated with disease, but not routinely measured. Antigens associated with organ damage: colours: frequently associated with disease, grey: controversial results or occasional observations.

Table 2: List of abbreviations

p-ANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
ANA	Anti-nuclear autoantibodies
BICLA	BILAG-based composite lupus assessment
BILAG	British Isles Lupus Assessment Group
c-ANCA	Cytoplasmic anti-neutrophil cytoplasmic antibodies
CCP	Cyclic citrullinated peptide
CDx	Companion diagnostics
DM/PM	Dermatomyositis/Polymyositis
dsDNA	Double stranded DNA
ENA	Extracted nuclear antigens
M2 Antigen	Anti-mitochondrial antibodies M2 complex
MCTD	Mixed connective tissue disease
NMO	Neuromyelitis optica
NPSLE	Neuropsychiatric systemic lupus erythematosus
pAPS	primary anti-phospholipid syndrome
PBC	Primary biliary cirrhosis
RA	Rheumatoid arthritis
SjS	Sjögren's syndrome
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index
SLICC	Systemic lupus international collaborating clinics
SSc	Systemic sclerosis

References

1. Roper G. Lupus Awareness Survey for the Lupus Foundation of America [Executive Summary Report]. 2012 [Available from: https://b.3cdn.net/lupus/2489f6ca2bcbde1818_ggm6i6gzi.pdf.]
2. Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology. 2017;56(11):1945-61.
3. LUPUS Foundation of America: Lupus facts and statistics [Available from: https://www.lupus.org/resources/lupus-facts-and-statistics.]
4. Pharmaceutical Technology: Top-grossing drugs in systemic lupus erythematosus and lupus nephritis 2020 [Available from: https://www.pharmaceutical-technology.com/comment/systemic-lupus-erythematosus-nephritis-drugs.]
5. Nasa. Challenges in SLE Drug Development: The Key Hurdles 2018 [Available from: https://decisionresourcesgroup.com/blog/challenges-sle-drug-development-key-hurdles/.]
6. Tselios K, Wakani L, Gladman D, Su J, Urowitz M, editors. Response to Placebo in Randomized Clinical Trials with Biologics in Non-renal, Non-neuropsychiatric Systemic Lupus Erythematosus: A Systematic Review and Pooled Analysis. ARTHRITIS & RHEUMATOLOGY; 2019: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.
7. Lockshin MD, Barbhaiya M, Izmirly P, Buyon JP, Crow MK. SLE: reconciling heterogeneity. Lupus science & medicine. 2019;6(1).
8. Sanz I, Lee FE-H. B cells as therapeutic targets in SLE. Nature Reviews Rheumatology. 2010;6(6):326.
9. Chan VS-F, Tsang HH-L, Tam RC-Y, Lu L, Lau C-S. B-cell-targeted therapies in systemic lupus erythematosus. Cell Mol Immunol. 2013;10(2):133-42.
10. Vukelic M, Li Y, Kyttaris VC. Novel Treatments in Lupus. Front Immunol. 2018;9:2658-.
11. Pike MC, Kelley L. Data quality challenges in systemic lupus erythematosus trials: how can this be optimized? Current rheumatology reports. 2012;14(4):324-33.
12. RheumatologyNetwork.com. Here's why there are no new treatments for lupus 2019 [Available from: https://www.rheumatologynetwork.com/view/heres-why-there-are-no-new-treatments-lupus.]
13. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis & Rheumatism. 2012;64(8):2677-86.
14. Bertsias GK, Pamfil C, Fanouriakis A, Boumpas DT. Diagnostic criteria for systemic lupus erythematosus: has the time come? Nature reviews Rheumatology. 2013;9(11):687-94.
15. Borchers AT, Naguwa SM, Shoenfeld Y, Gershwin ME. The geoepidemiology of systemic lupus erythematosus. Autoimmun Rev. 2010;9(5):A277-87.
16. Herbst R, Liu Z, Jallal B, Yao Y. Biomarkers for systemic lupus erythematosus. Int J Rheum Dis. 2012;15(5):433-44.
17. Ahearn JM, Liu CC, Kao AH, Manzi S. Biomarkers for systemic lupus erythematosus. Transl Res. 2012;159(4):326-42.
18. Gupta S, Tatouli IP, Rosen LB, Hasni S, Alevizos I, Manna ZG, et al. Distinct Functions of Autoantibodies Against Interferon in Systemic Lupus Erythematosus: A Comprehensive Analysis of Anticytokine Autoantibodies in Common Rheumatic Diseases. Arthritis & Rheumatology. 2016;68(7):1677-87.
19. Howe HS, Leung BPL. Anti-Cytokine Autoantibodies in Systemic Lupus Erythematosus. Cells. 2020;9(1):72.
20. Narain S, Richards HB, Satoh M, Sarmiento M, Davidson R, Shuster J, et al. Diagnostic accuracy for lupus and other systemic autoimmune diseases in the community setting. Archives of internal medicine. 2004;164(22):2435-41.
21. Watanabe A, Kodera M, Sugiura K, Usuda T, Tan EM, Takasaki Y, et al. Anti- DFS70 antibodies in 597 healthy hospital workers. Arthritis & Rheumatism. 2004;50(3):892-900.
22. Mahler M, Fritzler MJ. The clinical significance of the dense fine speckled immunofluorescence pattern on HEp-2 cells for the diagnosis of systemic autoimmune diseases. Clinical and Developmental Immunology. 2012.

23. Liu C-C, Kao AH, Manzi S, Ahearn JM. Biomarkers in systemic lupus erythematosus: challenges and prospects for the future. Therapeutic advances in musculoskeletal disease. 2013;5(4):210-33.

24. Hiepe F. Autoantibodies in systemic lupus erythematosus. Autoantibodies and autoimmunity Molecular mechanisms in health and disease Wiley-VCH, Weinheim. 2006:247-76.

25. Budhram A, Chu R, Rusta-Sallehy S, Ioannidis G, Denburg JA, Adachi JD, et al. Anti-cyclic citrullinated peptide antibody as a marker of erosive arthritis in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Lupus. 2014;23(11):1156-63.

26. Kirou KA, Lee C, George S, Louca K, Peterson MG, Crow MK. Activation of the interferon-- pathway identifies a subgroup of systemic lupus erythematosus patients with distinct serologic features and active disease. Arthritis & Rheumatism. 2005;52(5):1491-503.

27. Ching KH, Burbelo PD, Tipton C, Wei C, Petri M, Sanz I, et al. Two major autoantibody clusters in systemic lupus erythematosus. PloS one. 2012;7(2):e32001-e.

28. Villarreal G, Drenkard C, Villa A, Slor H, Shafrir S, Bakimer R, et al. Prevalence of 13 autoantibodies and of the 16/6 and related pathogenic idiotypes in 465 patients with systemic lupus erythematosus and their relationship with disease activity. Lupus. 1997;6(5):425-35.

29. Cambridge G, Isenberg DA, Edwards JC, Leandro MJ, Migone TS, Teodorescu M, et al. B cell depletion therapy in systemic lupus erythematosus: relationships among serum B lymphocyte stimulator levels, autoantibody profile and clinical response. Ann Rheum Dis. 2008;67(7):1011-6.

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