Testing Patients

The inherent complexity of clinical manifestations and variety of therapeutic responses has made treating autoimmune diseases like lupus especially challenging. However, with the rise of companion diagnostics, there could be a way to navigate these hurdles and achieve more positive outcomes

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Systemic lupus erythematosus (SLE) is an autoimmune disease affecting approximately five million people worldwide, yet the therapeutic options for patients remain limited. SLE is now significantly falling behind other autoimmune diseases – like rheumatoid arthritis – in terms of novel drug development, with the last half a century seeing only Benlysta® approved by the FDA.

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Development Barriers

It is well-known that B cells have a central role to play in the pathogenesis of SLE through a combination of antibody-dependent and -independent actions, resulting in tissue damage and the release of type 1 interferons (IFNIs) from dendritic cells. Clinical developments in this area have focused on the inhibition of autoreactive B cells in an attempt to reduce the production of autoantibodies. However, drug developers working towards an effective treatment for SLE face a number of hurdles:

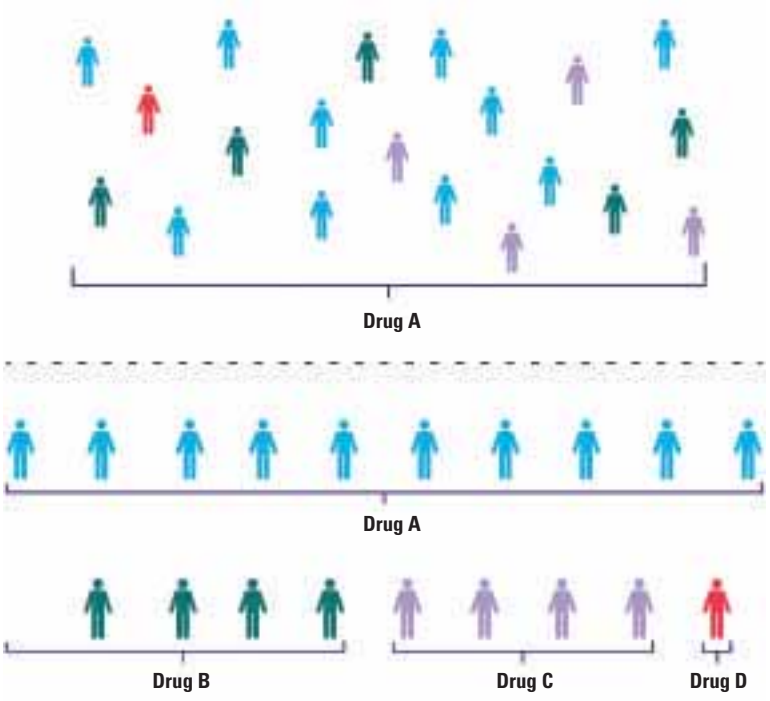
- There is currently no defined understanding of SLE pathogenesis, but it is accepted that a combination of predisposing genetic factors and environmental triggers play a part
- The remitting and relapsing nature of SLE means that patients enrolled in placebo arms of clinical trials for novel medicines still show significantly positive outcomes (1). Demonstrating considerable superior efficacy to the placebo is therefore a huge obstacle when seeking clinical and market approval
- SLE presents a variety of symptom profiles across multiple organs, suggesting it is a syndrome with the potential to be subdivided into smaller, more homogeneous groups based on biomarker patterns and disease characteristics
- The range of clinical presentations means that misclassification of SLE remains an issue, with misdiagnosis estimated to be as high as 20% (2). This also makes it especially difficult to apply composite responder indices in clinical trials

The degree of heterogeneity among SLE patients is a major challenge for pharmaceutical development, and remains something that the industry must overcome before effective and curative therapies can be identified. For this to happen, there is a clear need for both diagnostic biomarkers and assays that enable precise disease characterisation, patient stratification and response prediction.

Drug-Diagnostic Partnership

There has been growing concern over the 'one-size-fits-all' approach to drugs used in the treatment of autoimmune disease, which is in no small part due to the difficulty associated with identifying SLE subgroups. This general lack of

Figure 1: CDx can help combat the outdated 'one-size-fits-all' approach to autoimmune disease treatment. Where normally all patients would be given a single drug (top panel), CDx allows for the identification of different drug response groups (bottom panel), leading to each group receiving personalised therapy



patient stratification means that a drug designed to manage specific symptoms can have a range of effects in different patients, based on an individual's genetic predisposition and unique physiological responses; most drugs used to treat autoimmune diseases show a maximum response rate of 50% (3).

Companion diagnostics (CDx) are the much-needed biomarkers required to pinpoint those with an increased likelihood of responding to treatment and effectively stratify patients (see Figure 1). The ability to define true SLE patients – and also dissect SLE into different subgroups using specific patterns of biomarkers and organ involvement – will be particularly important in evaluating therapeutic efficacy across clinical trials (1,4). While CDx have been used primarily in oncology – for example, Herceptin® with its CDx, HER-2/neu – their value is abundantly evident, and they have received guidance and support from regulatory bodies such as the FDA (5).

Ideally, CDx development should take place during the earliest phases of drug development; partnering with early SLE programmes has the potential to drastically alter the outcome of prospective treatments. A co-development model like this also has added benefits:

- Patient selection based on biomarker data means that the prescribed trial endpoints are more likely to be achieved
- The chance that a drug will gain regulatory approval is increased, ultimately saving significant time and financial costs
- Data from CDx can result in drugs being brought to market much quicker: Zelboraf® and Xalkori®, both of which were approved with their respective CDx, reached the market less than five years after entering clinical trials. This is in part due to the robust data generated from the development of their CDx

In addition, multiple stakeholders can expect the following:

- CDx open up valuable market opportunities for those working on the identification and development of clinically relevant biomarkers. The in-depth research into specific disease areas leads to greater insight into disease pathogenesis and progression – potentially resulting in the discovery of novel targets, biomarkers or treatments
- CDx will allow healthcare providers to prescribe drugs more accurately and tailor therapies to the individual, thereby enhancing clinical utility
- Payers benefit thanks to CDx discriminating between different patient subsets by highlighting those groups eligible for a particular drug, while excluding others. This serves to save the healthcare system unnecessary costs and enables patients to access treatment earlier

The advantages associated with the use of CDx make this a market with high potential for revenue generation. Despite still being in its infancy, the global CDx market is expected to reach $3.5 billion by 2020, with a predicted compound annual growth rate of 20% between 2014 and 2020 (6). These figures do not take into account autoimmune diseases like SLE, and predictions could be exceeded by the growing body of research into this disease area and corresponding CDx.

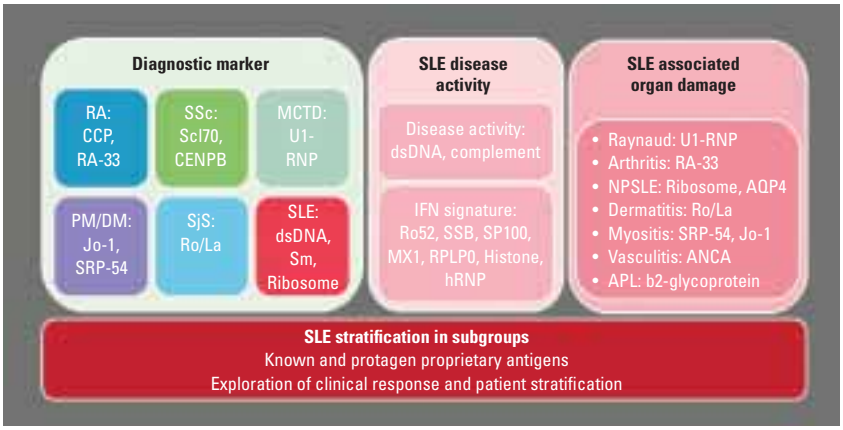
Stratifying Patients

In order to develop CDx for targeted SLE therapies, it is first necessary to overcome the inherent heterogeneity among SLE patients. This is achieved through three principal steps, leading to successful stratification and the identification of distinct subgroups (see Figure 2).

The initial stages require identifying an appropriate SLE patient population. Traditional anti-nuclear antibody (ANA) tests alone are insufficient as they are not specific for SLE: ANAs occur in other rheumatic and infectious diseases, as well as being present in up to 20% of the general population (7). Anti-double stranded DNA tests, on the other hand, are more precise for SLE, but are less sensitive (30-70% compared to up to 98% with ANA tests). However, they are present in less than 1% of healthy individuals, making them valuable for confirming an SLE diagnosis.
To characterise patients that do not exhibit symptoms specific to SLE alone, but have overlapping features with other rheumatic/autoimmune disorders, it becomes necessary to include additional diagnostic antigens, such as the anti-cyclic citrullinated peptide (CCP). Identifying a homogenous group of SLE patients therefore requires a suite of diagnostics, including antibody reactivity and the detection of autoimmune antigens.

The next step in stratifying SLE patients involves the identification of those patients with a high level of disease activity. In sufferers, dendritic cells can be activated by DNA-containing immune

Figure 2: The diagnostic steps required to identify appropriate SLE patient populations, determine those with a high level of disease activity and predict specific SLE-associated organ damage. Stratification in subgroups supports the concept of personalised medicine



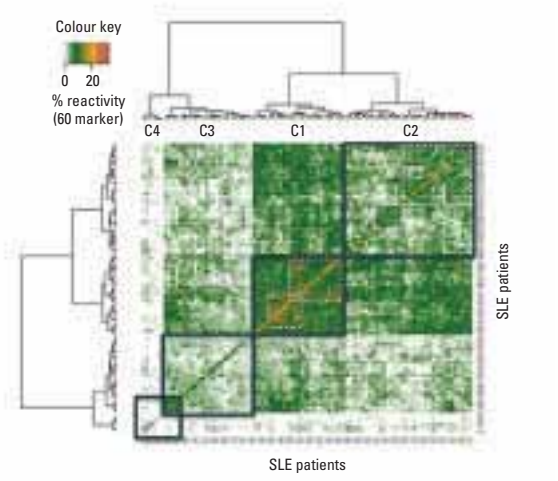
complexes, causing them to release IFNIs in response to tissue damage (8). The more severe diseases are associated with high levels of interferon-induced gene expression and specific autoantibody patterns. Elevated levels of anti-dsDNA and anti-C1q antibodies, for example, are associated with lupus nephritis preceding flare-ups of disease activity. Activation of the interferon (IFN) pathway and a characteristic pattern of autoantibodies that target IFN-inducible genes can, therefore, be used as a diagnostic tool to provide information on disease activity.

With an appropriate SLE group identified and the disease activity assessed, the last steps involve predicting SLE-associated organ damage. This can also be determined by evaluating distinct autoantibody profiles. For instance, high levels of anti-U1-RNP autoantibodies are associated with Raynaud's phenomenon and reduced probability of nephritis; combined anti-Ro/La antibodies are associated with secondary Sjögren's syndrome and photo-sensitivity, but a lower risk of nephritis; and anti-ribosomal P antibodies are associated with central nervous system lupus.

Assembling The Pieces

With this diagnostic framework, it should be possible to stratify SLE into distinct subgroups. The NavigAID SLE is a stratification array based on a solid database of more than 700 SLE patients (>1,000 serum samples), combining 87 selected known and proprietary biomarkers. It is presently capable of successfully characterising four SLE patient subgroups/clusters (see Figure 3).

Figure 3: A contingency heat map of SLE patients in which the number of positive autoantibodies per SLE patients is presented as a colour code – from 0 (green) up to 60 (red) autoantibodies. This highlights the stratification of SLE patients into four subgroups (C1, C2, C3 and C4)



This system distinguishes between SLE patients, ranging from a highly reactive group who have a high disease activity score and possess broad and homogenous positive autoantibody reactivity, through to a smaller cluster who have comparatively low levels of autoantibody reactivity. Labelled as C1 through to C4, there are further subdivisions of C1 into patient subgroups with a mutually exclusive autoantibody profile. Group C4 includes putative 'outliers' who present themselves with reactivity towards partially unique markers.

The co-appearance of multiple autoantibodies in SLE patients has rarely been analysed (9,10). However, this has now been examined in substantially greater detail, and has proven to be invaluable for defining more homogeneous patient groups and solving the problem of heterogeneity in SLE.

Following on from these foundations, it is hoped that the industry will begin to align CDx development with clinical programmes for SLE treatment, benefiting from the highly relevant patient stratification. A greater emphasis on this co-development model, bringing together CDx and drug development, will allow for a much greater understanding of the disease in the earliest possible stages. This can result in the earlier identification of possible side-effects, a shortening of overall trial lengths, and numerous improvements to drug efficacy and safety.

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