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May you live in interesting times: challenges and opportunities in Lupus research

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“It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us....”. Charles Dickens, *A tale of two cities*

In reflecting on the state of affairs in lupus research one could be forgiven for recalling Dickens’ introduction to one of his best known novels. After all, research into the pathogenesis and treatment of lupus can resemble a rollercoaster with an ever growing number of promising leads turning into apparent dead ends and disappointment as recently illustrated yet again by the failure of phase III trials of drugs with strong scientific rationale and promising phase II results (epratuzumab)¹ or lack of efficacy signals in early studies of well-documented pathways (anti- IFN γ)². The failure of epratuzumab to meet the primary endpoint in the EMBLEM study was particularly bitter given that this anti-CD22 antibody targets activated mature B cells, long- thought to play a pathogenic role in SLE thereby extending previous negative results with anti- CD20 antibodies. Despite the approval and rather extensive clinical use of belimumab, additional questions about the efficacy and best utilization of anti-B cell agents are also raised by negative or inconsistent results obtained with other antagonists of TNF superfamily receptors that regulate B cell tolerance, activation and survival including atacicept (TACI-Ig fusion protein blocking BLyS and APRIL) and tabalumab (human IgG4 mAb binding soluble and membrane- bound BLyS)². All the while, there continues to be a great need for better treatments as indicated by evidence that even in the 2000’s the risk of end-stage renal disease may be over 40% over 15 years in class IV lupus nephritis³, and by the rarity of sustained disease remissions with only 15% of patients staying in complete remission for 3 years and less than 4% achieving this desirable outcome for more than 10 years^{4, 5, 6, 7}.

The difficulty with clinical trials in SLE

Two main problems are likely to account for the lack of expected efficacy of B cell therapies and other agents in SLE. First, conventional clinical trials have suffered from significant drawbacks including short duration, efficacy of background therapy, outcome measurements

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and the magnitude of the placebo effect among others. These topics have been extensively discussed elsewhere and will not be further considered here ^{8, 9, 10}. Secondly, SLE is a highly heterogeneous disease in which separate clinical manifestations and accordingly, therapeutic responses may be mediated by distinct mechanisms. Hence, this perspective is focused on the difficulties and opportunities afforded by our growing understanding of the complexity of the disease process itself as it is imperative that we dissect disease heterogeneity in ways that are relevant to therapeutic decisions ⁹. As summarized in this opinion piece, an integrated analysis of recent progress offers ample reason to be optimistic while also providing a roadmap for future efforts. Arguably, everything should be before us.

Advances in SLE research

An optimistic view of lupus research is supported by a continuously growing understanding of disease pathogenesis more recently illustrated by studies of new pathogenic and regulatory cells and mechanistic pathways (summarized in Table 1). Moreover, the field also benefits from an unprecedented ability to interrogate these players individually and at the system level through technologies with the power to identify complex patterns and discover unheralded emergent features ^{11, 12} (Illustrated in Figure 1). Thus, immune repertoires can be dissected in large scale through cellular Next Generation Sequencing, ultra-high throughput single cell monoclonal antibody generation and serum autoantibody proteomics ^{13, 14}. In turn, an array of OMICs technologies, including transcriptomics, genomics, proteomics and metabolomics to just mention some, permit unsupervised cellular and molecular analysis of disease components. Together, the combination of improving technology and bioinformatics offers unprecedented opportunities to integrate molecular programs and immune function while at the same time discovering cellular heterogeneity through single cell interrogation ¹⁵.

New therapeutic targets in SLE

Growing experimental prowess is complemented by the ability to generate drugs tailored to specific cells or molecules and *in silico* analysis of public data can be applied to repurpose for the treatment of SLE, drugs currently available for other diseases ¹⁶. As a result, areas of major therapeutic promise continue to develop to target different cellular and molecular targets (summarized in Table 2), including direct cytokine inhibition, a strategy exemplified by belimumab, the first biological ever developed and approved for SLE ¹⁷.

Targeting interferons in SLE

Currently, cytokine inhibition is best illustrated by IFN blockade an approach supported by genetic and transcriptional studies and a growing understanding of innate sensing pathways and downstream effectors ¹⁸. The rationale for IFN blockade has also been enhanced by the recognition of several Mendelian type I interferonopathies with lupus-like manifestations ¹⁹. While initial studies of narrow anti-IFN α antibodies (rontalizumab) were disappointing, sifalimumab, an antibody capable of neutralizing most IFN α subtypes achieved its primary efficacy endpoint (SRI of 4 at 365 days) despite a high placebo effect (45.4%), and the fact that these agents fail to inhibit IFN β , another type I IFN of growing significance and

pathogenic potential^{20, 21}. In keeping with this concept, promising results have been reported for anti-IFN receptor antibodies that should inhibit signaling by all type I IFNs. Thus, in a phase II study of 351 SLE patients with moderate to severe disease activity and inadequate response to standard of care (MUSE), treatment with anifrolumab, a human IgG1k monoclonal antibody directed against the subunit 1 of the type I IFN receptor, met the primary efficacy endpoint (SRI 4 response at day 169) for the lower dose of 300 mg in the context of a lower placebo response (17.6% versus 34.3% for anifrolumab). Anifrolumab also met its secondary SRI endpoint at day 365. Updated results from this study presented at EULAR 2016 also indicate that global type I IFN blockade can ameliorate disease in multiple organ domains² including skin and musculoskeletal manifestations and suggestive trends in cardiorespiratory, vascular, hematological and constitutional domains. Anifrolumab also improved immunological biomarkers and reduced the need for glucocorticoids². Nevertheless, while highly promising, these studies again portend an inevitable variability in response. Not surprisingly, this variability may be determined in part by baseline IFN activity as anifrolumab suppressed the IFN gene signature (IFNGS) more strongly than sifalimumab²² and patients with a high IFNGS fared better in the MUSE study.

Owing to the significance of the IFN pathway, multiple other strategies to inhibit either the production or the activity of this cytokine family are currently under development. As illustrated in Table 2, potential approaches include targeting of plasmacytoid dendritic cells; inhibition of TLR and other nucleic acid sensors and JAK-STAT inhibitors of IFN signaling²³.

Understanding disease heterogeneity

As the scientific community and the pharmaceutical industry continue to make strides in multiple therapeutic areas, it seems inescapable that the central challenge faced by lupus researchers is how to assemble all the pieces into a coherent quilt in order to enhance the benefit of current therapies and inform new strategies⁹. In particular, it is imperative that we dissect disease heterogeneity in ways that are relevant to therapeutic decisions⁹.

While the clinical heterogeneity of SLE has long been recognized, the underpinnings and by extension, the biomarkers of variable clinical manifestations and therapeutic responses remain poorly understood. Lupus heterogeneity is surely determined by the assortment of susceptibility genetic variants in individual patients and by poorly known epigenetic modifications^{24, 25}, the endogenous microbiome²⁶ and environmental elements including biological and chemical factors and social stressors. To further complicate the picture, heterogeneity is also likely to be enhanced by disease stage (early versus late and acute versus chronic) and to contribute to diverse outcomes not only through the induction of distinct pathogenic pathways but also through differential engagement of repair and compensatory mechanisms, a factor that may be critical in lupus nephritis²⁷.

Appropriately then, growing efforts are being applied to deciphering lupus heterogeneity in all those fronts starting with genetic studies that now encompass multiple ethnic groups and have, through the use of whole genome sequencing, a much greater ability to discover individual genetic variants with either pathogenic or protective effects^{28, 29}. It stands to

reason that we need to integrate complementary approaches in order to fully understand the confluence of genetic variants, epigenetic regulation and the endogenous and exogenous environments. Accomplishing these goals is certainly within our reach through a combination of high- throughput –omics technologies including genomics, transcriptomics, proteomics and metabolomics, as well as state-of-the-art cytometry, all tools of proven ability to decipher and even predict immune responses ^{12, 30} (Figure 1).

Undoubtedly, these efforts are starting to paint a much more nuanced picture of individual genetic variability and of its functional consequences in ways that should be incorporated in the near future into study design and therapeutic decision making. To date, global transcriptomic analysis has contributed the most to our ability to segment lupus patients and identify severe disease although some studies have not found a correlation between the global IFN signature and ^{31, 32}.

More recently, sophisticated modular analyses of whole blood transcriptomics data have unveiled an unprecedented level of disease heterogeneity in a longitudinal cohort of pediatric patients ³³. Multiple molecular modules identified a global lupus profile defined by IFN, neutrophil, inflammation, cell cycle, erythropoiesis, and histone modules. In at least a subset of samples, a plasmablast (PB) signature provided the best association with disease activity measured by SLEDAI. In contrast, a neutrophil signature was enriched in patients with nephritis and distinctive modular differences could be detected between untreated proliferative and membranous nephritis and between the two types of nephritis after treatment with mycophenolate mofetil. Finally, weighted gene co-expression network analysis (WGCNA) of longitudinal samples established correlations between transcriptional modules and disease activity and different clinical manifestations in individual patients. This strategy stratified SLE patients into 7 groups on the basis of distinct combinations of five immune signatures correlating with the SLEDAI, including erythropoiesis, IFN response, myeloid lineage/neutrophils, plasmablasts, and lymphoid lineage. Moreover, the analysis of hundreds of WGCNA modules was able to identify individual correlates with singular clinical and laboratory manifestations thereby raising the tantalizing possibility of personalized immune-monitorization and by extension precision therapy.

Global transcriptional analysis also provides a promising way to understand the heterogeneity of inflammatory pathways in lupus nephritis ³⁴.

Experimental challenges and opportunities

It is important to note that different mechanisms may be identified through transcriptomics analysis of purified cell fractions, a strategy able to pinpoint patterns that may be obscured by the relative abundance of different populations in whole blood ^{35, 36, 37, 38}. In particular, fractionated analysis has identified transcriptional signatures of activated CD8 memory T cells as the strongest predictor of disease prognosis without correlation with ongoing disease activity, in both SLE and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis ³⁶. Moreover, poor prognosis was ascribed to the engagement of the IL-7R pathway. These data are in keeping with previous demonstrations of the prominence of activated CD8 T cells in active SLE and the correlation between intra-renal CD8 T cells and

poor outcome in proliferative lupus nephritis³⁹. Follow-up studies have formulated an important mechanistic paradigm invoking the inability of chronically stimulated autoimmune CD8 memory T cells to establish programs of cellular exhaustion similar to those induced by chronic viral infection³⁵. Hence, the combined evidence points to IL-7R-high CD8 T cells as an attractive therapeutic target either for elimination or modulation. The latter goal could be accomplished in several ways including IL-7R receptor blockade as initially investigated in Multiple Sclerosis and currently in type 1 diabetes⁴⁰ or by enforcement of negative regulatory checkpoints⁴¹, both interventions that might induce conversion from activation to exhaustion. It is also interesting to consider that, at least in some models, the absence of B cells promotes the death of activated CD8 T cells⁴² and that in keeping with that role, B cell depletion-induced changes in CD8 T cells have been postulated as a mechanism of action for rituximab in several autoimmune diseases including SLE⁴³.

Translating heterogeneity into better and more specific treatments

It is therefore clear that agnostic studies can reveal significant biological variability in SLE patients, narrowly identify new therapeutic targets and guide their application to a suitable disease segment. At the same time, the striking level of heterogeneity being unearthed should make us ponder how to incorporate increasing levels of segmentation into clinical trials design and ultimately, into actionable therapeutic decisions. Are we going to Heaven or rather in the opposite direction?

Ultimately, an integrated effort between scientists and clinicians will be required to design clinical trials based on biological segmentation (Figure 1). The most productive scenario would require incisive, relatively small, mechanistically informed phase II trials to assess the benefit of targeting specific pathways in well-defined disease subsets. I believe however that before this can be done with confidence a number of challenges will have to be overcome. First, validation of extant information and a more definitive association of biological pathways with disease subtypes and different outcomes will have to be established through in-depth study of well-characterized patient cohorts and the use of clinical measurements and outcomes beyond the imprecise information provided by the SLEDAI and similar instruments. In the end however, while these approaches will clearly unravel disease heterogeneity in SLE, they are also unlikely to adjudicate causality, a goal that may require extensive functional studies and in-depth characterization of clinical responses to specific agents. In particular, it can be argued that incisive mechanistic sub-studies should be conducted in both poor responders and in elite responders even when the latter may represent a relatively minor fraction of patients in negative clinical trials. Unfortunately, this continues to be an elusive area of research as many clinical studies suffer from lack of in-depth mechanistic studies.

Nevertheless, some important principles can be gleaned from extant studies. Thus, it seems apparent that even within discreet patient groups multiple pathways are engaged in active disease. If so, it follows that in order for monotherapy to successfully induce disease remission we would need to identify shared upstream triggers of these pathways. Otherwise, we would be bound to use pleiotropic agents, including glucocorticoids or agents capable to

inhibit multiple cytokines as indicated in Table 2, to induce remission and/or to minimize damage while remission is attained by more specific agents. Alternatively, it is possible that combination therapy with multiple agents may be required at least for remission induction and clinically, for rapidly progressive disease. A corollary is that precision strategies with single agent, pathway- specific approaches might be better suited for maintenance therapy and individualized preventive interventions aimed at avoiding flares or averting disease development in high-risk populations. Accordingly, these considerations should be part of clinical trial design and interpretation. Specifically, the level of information generated by the technologies previously mentioned provide a unique opportunity for innovative adaptive design trials informed by precise mechanistic measurements of susceptibility and response to different agents ⁴⁴.

In closing, we must believe that this is the best of times for Lupus research. The field continues to generate insightful technological and scientific advances and to generate new data that are publically available for analysis. We also benefit greatly from strong clinical and research consortia, patient advocacy and support and patients cohorts encompassing most ethnic groups in the US (<http://www.cdc.gov/lupus/index.htm>), and around the world ^{45, 46, 47, 48} and unprecedented capability for targeted drug design. Epidemiology, outcomes and disparity research continue to make great strides ⁴⁹ and philanthropy keeps on growing (<http://lupusresearchinstitute.org/lupus-news/2016/07/14/three-leaders-lupus-merge-form-lupus-research-alliance>). Unquestionably however, challenges remain to ensure continuation and expansion of progress. Concerted efforts such as the recent Accelerating Medicine Partnership (AMP; <https://www.nih.gov/research-training/accelerating-medicines-partnership-amp>), should pursue enhanced and streamlined collaborations between academia, government and industry. Also important will be improved patient participation in clinical trials. Last but in no way least, it will be critical to ensure that current funding trends and overall research support by medical schools and academic health care systems do not compromise our ability to attract, train and retain the best young minds into Lupus research.

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Figure 1.
Translating disease heterogeneity into targeted therapies

Table 1

New mechanistic insights of relevance to SLE research

Phenotype and function of pathogenic and regulatory cells	B cells and plasma cells ^{13, 50, 51, 52, 53, 54, 55} T cells ^{56, 57, 58, 59} Myeloid cells ^{27, 54, 60, 61, 62, 63, 64}
Understanding disease progression	Early events leading to disease development ^{21, 65} ; mechanisms of end-organ damage and repair ²⁷ in situ adaptive and innate immune reactions in the kidney ^{66, 67}
Antigenic triggers	DNaseI sensitive apoptotic particles ⁶⁴ Endogenous DNA ⁶⁸ Oxidized mitochondrial DNA ^{62, 63} Ro60 and endogenous retroviruses ⁶⁹ Apoptotic cells as inducers of autoreactive TH17 cells ⁷⁰
Inflammatory loops	Innate and adaptive pathways ⁷¹ Nucleic acids and new inducers of the interferon pathway ^{62, 63, 69, 72, 73} Inflammasome ⁷⁴ .

Table 2

New and emergent therapies for SLE

B cell and plasma cell targeting	New B cell depletors ^{2, 75}	
	B cell receptor signaling inhibitors ^{76, 77, 78}	
	Histone deacetylase inhibitors ⁷⁹	
	Plasma cell depletors ⁸⁰	
T cells	T helper cell modulation (Laquinimod) ²	
	Calcineurin inhibitors ²	
	Inducing CD8 T cell exhaustion through IL-7R or enforcement of inhibitory checkpoints ^{40, 41}	
Modulation of co-stimulatory pathways	CD40L (CD154) blockade ²	
	ICOS-L blockade ²	
Enforcement of tolerance checkpoints	PD-1 and other inhibitory pathways ⁴¹	
Inhibition of the NLPR3 inflammasome ⁷⁴		
Blockade of Toll-like Receptors (TLR) and other RNA and DNA sensors ²³		
Cellular therapies	Regulatory T cells and B cells and Mesenchymal Stem Cells ^{81, 82, 83}	
	<i>In vivo</i> induction of regulatory T cells by low-dose IL-2 ⁸⁴	
	Antigen-specific cytotoxic CAR-T cells ⁸⁵	
	Antigen-specific regulatory CAR-T cells ⁸⁶	
Cytokine inhibition	BAFF ²	
	IFN blockade	anti-IFN and anti-IFNR antibodies ²
		Jak kinase inhibition (tofacitinib Baricitinib) ²³²
		pDC depletion (PCDA2 and CD123 antibodies; Bcl2 inhibition) ²³
	Multiple cytokine inhibition	Jak Kinase inhibition (Baricitinib: type I and II IFN; IL-6; IL-23; GM-CSF; and IL-12). ²³
IL-21, IL-6, IL-12/23, others ⁸⁷		