VIEWPOINT

Reflections on Lupus 2013: butterflies, wolves and prophecies

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The recently concluded Tenth International Congress on Systemic Lupus Erythematosus (SLE) held in Buenos Aires was a resounding success. This overview summarizes some of the origins of the First International Congress held in Calgary, Canada in 1986, predictions offered by past Congress Presidents, and a perspective on the trends in autoantibody testing, which remains one of the key approaches to the early and accurate diagnosis of SLE. The last few decades have witnessed a remarkable proliferation of new diagnostic technologies including addressable laser bead immunoassays and, more recently, chemiluminescence and lateral flow technologies that could find a clinical niche in point-of-care diagnostics. Against the backdrop of these constantly emerging technologies, indirect immunofluorescence has remained the platform of choice for many laboratories and diagnosticians. The notion that autoantibodies are pathogenic has been challenged by evidence that some autoantibodies are protective, some may have catalytic capacity while others may be neutral or have no function at all. The latter notion of functionless or “junk” autoantibodies needs to be taken under some advisement, because there was a time when a great proportion of the human genome was considered to include “junk DNA”. The butterfly as a symbol of hope and progress in SLE research over the past 27 years since the First International Congress on SLE is almost certainly to be even more appropriate when future Congresses are held in Geneva (2015), Melbourne (2017) and eventually one in 2050. Lupus (2013) 22, 1092–1101.

Key words: Systemic lupus erythematosus; review; congress; autoantibodies; butterfly

Introduction

The Tenth International Congress on Systemic Lupus Erythematosus (SLE) has recently concluded in the magical city of Buenos Aires, Argentina. This congress was primarily organized under the capable leadership of Dra. Mary Carmen Amigo (Mexico) and Dr. Bernardo Pons-Estel (Argentina), with the assistance of Dra. Eloisa Bonfà (Brazil) and the GLADEL Executive. One, but not the only, measure of success was the all-time high in attendance of more than 1800 attendees accompanied by 363 abstracts and posters.

A unique feature of the Congress was the participation of past hosts (aka ‘presidents’) of the previous SLE Congresses, in an Opening Session during which they had been challenged to provide a brief prediction of the state of clinical practice and/or science in their areas of interest related to SLE in 2050. Dr. John Esdaile, President of the 2010 meeting in Vancouver, spoke to cardiovascular disease in SLE and predicted that it would be eliminated by 2050. Dr. Munther Khamashta (President of the 2001 meeting in Barcelona) predicted that morbidity and mortality attending high-risk pregnancies in SLE would be addressed by artificial womb technology. Dr. Graham Hughes (President of the 1992 meeting in London) spoke by video link and predicted the resolution of antiphospholipid syndrome. Dr. Yehuda Shoenfeld, President of the 1995 meeting in Jerusalem, spoke about the future of the ASIA syndrome (Autoimmune Syndromes Induced by Adjuvants); autoimmune diseases following adjuvanted vaccines and diffused silicone implants. Since the most prevalent and most notorious adjuvant in vaccines is aluminum, Dr. Shoenfeld envisioned that this substance will be eliminated from and replaced with safer ones in vaccines within the next 50 years. Similarly, the silicone material which at one time was believed to be inert to the immune system and chronically stimulates the immune system inducing a facet of ASIA syndrome, which may evolve into
more defined autoimmune (rheumatic) disease, will be replaced by a safer material or by better devices which do not leak. Dr. Bob Lahita (President of the New York meeting in 2004) via video link reminded us that SLE is the prototypic autoimmune disease and remains at the forefront of advances in modern biology. His hope was that any advance in understanding this illness will benefit those with related illnesses such as multiple sclerosis, Sjögren’s syndrome and polymyositis.

It was a pleasure to attend the meeting, and as the President of the First International Congress on SLE held in Calgary in 1986 I thought it timely to reflect on the origin of the Congress, its progression and then to provide a perspective on antinuclear antibody (ANA) testing in the year 2050.

Genesis of the SLE International Congress

The meeting held in Calgary was the product of a vision of the co-chair Dr. Eng M. Tan, who felt that medical congresses at the time had become focused on more prevalent diseases such as rheumatoid arthritis or osteoarthritis, or had become deeply immersed in the molecular aspects of cellular and molecular immunology without much attention devoted to SLE itself. It was clear that although SLE was regarded the prototype for multi-system autoimmune diseases, attention to the disease and the patients had not achieved high visibility in the research, clinical or lay communities. Calgary had the good fortune to have one of the very first highly organized patient advocacy groups, the Lupus Erythematosus Society of Alberta (LESA), which was founded by Dr. Ian Watson and a small group of patients in 1973. Prior to coming to the University of Calgary in 1972, Dr. Watson was a post-doctoral fellow with Dr. Frank Dixon at the Scripps Clinic and Research Institute in La Jolla, California, where he worked on lupus nephritis. After his untimely passing in 1978, an annual award bearing his name was instituted by LESA and is given to a Canadian trainee who demonstrates exceptional quality research on SLE. LESA also became the stimulus for the eventual formation of Lupus Canada and similar patient advocacy groups around the world. Suffice it to say that, from the beginning, patients have been an integral and dynamic part of the Lupus congresses. Certainly, the meeting in Buenos Aires was no exception: over 300 patients and their advocates met alongside clinicians, scientists and industry sponsors. By comparison approximately 30 patients participated in the Calgary meeting. This tenfold increment over the 27 years since the first Congress was also reflected in overall attendance in Buenos Aires: 175 attendees in Calgary and over 1800 in Buenos Aires.

Of butterflies and wolves

The logo for the meeting in Calgary and every one that followed, including, the one just concluded in Buenos Aires has been the symbol of the butterfly (Figure 1). I believe that it is important to document the reason why the butterfly was initially chosen because, at first glance, most observers assume that it is merely a reflection of the imagery of the butterfly rash that characterizes some SLE patients. While that image was in mind, I chose the butterfly logo based on the Greek myth of Pandora’s Box.

According to Greek mythology, Zeus, the father of gods and men, ordered Hephaestus, the god of craftsmanship, to create Pandora, the first woman...

Figure 1  The butterfly logos of the First International Congress on SLE held in Calgary, Canada in 1986 and the most recent Congress held in Buenos Aires.
on Earth. She was endowed with many gifts: clothed Athena, endowed with great beauty by Aphrodite, and eloquent speech by Hermes. After Prometheus stole fire from heaven, Pandora was given a beautiful container by Epiphemus, Prometheus’ brother. Pandora was given explicit instructions not to open the container under any circumstance. However, another of her god-given traits, curiosity, eventually got the better of her and she opened it only to find that all evil escaped and afflicted the entire earth. Realizing her error, she tried to make amends by closing the container, but the entire contents had escaped, except for one thing – a winged creature with iridescent wings – the personification of Hope named Elpis.6,7

What captivated my attention in the Pandora’s Box myth was that the last creature to come from the box had iridescent wings (i.e. butterfly), the symbol of hope. Certainly, when a patient is diagnosed with SLE, it seems that Pandora’s box is opened because “all evil” seems to break loose. However, as aptly represented in the symbol of the butterfly, the SLE Congresses over the past 27 years have clearly shown that for patients, their families and health care providers there is reason for optimism and hope.

The butterfly as a symbol of hope is offset by the more sinister symbol of the wolf.5 A thorough historical account of the derivation of the term “lupus” and “lupula” is provided by Benedek,8 who opines that understanding how SLE became associated with this carnivore is “obscure”. A link to the wolf has never been clear to me either, particularly the notion that the nomenclature was chosen because certain SLE skin lesions resembled a “wolf bite”.5 I have not seen a Canis lupus (wolf) bite, but I have seen numerous bites of its near relative Canis canis (domestic dog), even on the face of my eldest daughter, and can find no resonance with the skin lesions of lupus. I wonder if the lupus nomenclature is more aptly related to the sinister appearance of the wolf, and the periopic “mask” that has a distribution similar to the “butterfly rash” of SLE. Or, perhaps, the metaphor might be traced to one of the oldest texts in the world, the Babylonian epic Gilgamesh, where the lead character rejects the sexual advances of the goddess Ishtar, reminding her that she had transformed a previous lover, a shepherd, into a wolf, thus turning him into the very animal that his flocks must be protected against (not a bad metaphor for autoimmunity). And, according to Avesta, the sacred text of the Zoroastrians, wolves were a creation of the evil spirit Ahriman, and are ranked among the most cruel of animals.9 Whatever the original nomenclature had in mind,5,8 I preferred the symbol of the butterfly rather than the wolf, although a bronze sculpture by Beverly Steigerwald that was commissioned for the First International SLE Congress as a gift to keynote speakers, embodied both the butterfly and wolf imagery (Figure 2).

ANA in 2050

The butterfly as a symbol of hope is an excellent segue to the topic assigned to me by the organizers...
of the Buenos Aires meeting: “What will ANA (anti-nuclear antibody) testing be like in 2050?” At first glance, 2050 seems like an impossibly long time gap to ponder, but I was reminded that 27 years had already passed since the first SLE Congress and 2050 lies a mere 37 years in the future! While I am tempted to recount the progress in SLE autoantibody research over the past 27 years, it is more challenging to consider the future. There is a well-known aphorism that says “Prediction is difficult, especially when it involves the future”.

In thinking about the future of ANA testing, I think it important to consider the current trajectory of medical care. In my opinion, there is no doubt that medical care is progressing to what in contemporary parlance is referred to as personalized medicine (reviewed elsewhere,\(^{10,11}\) a concept and paradigm that goes by a number of other names (Table 1)). I am particularly convinced that this is a part of the desired future for SLE, primarily because the disease is remarkably heterogeneous and a “one size fits all” approach to SLE therapeutics seems rather naïve. Numerous presentations in Buenos Aires reminded us of the “dark side” of one size fits all for SLE, especially the prevalent use of corticosteroids and their attending constellation of side effects,\(^{12}\) and also a newer generation of medications such as belimumab where, regardless of dose, the SLE Response Index at week 52 hovers around 50%.\(^{13,14}\) This and newer generation therapies for SLE need to be tailor made and prescribed for subsets of lupus.\(^{14,15}\) There are several existing paradigms that already use this approach; one of the best known is the approach to treatment of breast cancer based on tumor and other genetic markers such as human epidermal growth factor 2 (HER2) and BRCA1/2.\(^{16}\)

Subsets of SLE are on the one hand intuitive (i.e. subacute cutaneous lupus, lupus nephritis, neuro-psychiatric lupus, anti-phospholipid, etc), but on the other hand challenging because of extensive disease overlap. Anticipation was high that a genomic map of SLE\(^{17}\) would clarify etiology and pathogenesis. Notably, current evidence suggests that autoantibodies are a “window” to many of the genetic markers identified to date.\(^{18}\) Thus, there is reason to expect that subsets of SLE, perhaps based on autoantibody profiles, are a key to more effective future therapies and interventions.\(^{19-21}\)

The technologies and diagnostic platforms that are available to detect ANA and related autoantibodies have grown remarkably in the last decade, dating to the LE cell test in the 1950s, to indirect immunofluorescence in the 1960s, immunodiffusion, enzyme linked immunoassays (ELISA),\(^{22-24}\) dot blots,\(^{25,26}\) line immunoassays (LIA),\(^{27,28}\) and more recently multiplexed immunoassays such as addressable laser bead immunoassays (ALBIA),\(^{29,30}\) antigen arrays on planar surfaces,\(^{31-33}\) nanobarcodes,\(^{34}\) chemiluminescence\(^{35}\) and lateral flow and other point-of-care diagnostics,\(^{36}\) and other promising new technologies that continue to emerge (Table 2) (reviewed in Fritzler\(^{37}\)). The ability to detect over 30 autoantibodies in a single pinprick blood sample is commonplace today, and technologies such as nanobarcodes are said to increase that capacity by more than 2000 fold (up to 80,000 analytes).\(^{29,30,34}\) Modern diagnostic laboratories have adopted many of these technological advances because they are amenable to automation, high-throughput testing, are increasingly inexpensive, and have rapid turn-around times, and/or are adopted in point-of-care settings. With the emergence of new diagnostic technologies, it is clear that changes are needed in how the diagnostician and clinician interpret the test results. For one thing, the results from any one of the new immunoassay technologies can be at considerable variance with older technologies, or even between newer technologies. In particular, this has

### Table 1 Personalized medicine also known as (AKA)

- Individualized Medicine
- Designer Medicine
- Molecular Medicine
- Prospective Medicine
- Prescriptive Medicine
- Theranostics: Therapeutics/Diagnostics
- Translational Genomics
- Person-Centered Medicine

### Table 2 Conventional and emerging technologies for clinical autoantibody testing

- Line Immunoassays (LIA)/Dot Blot Immunoassays (DBIA)
- Antigen Arrays on Planar Surfaces
- Addressable Laser Bead Assays (ALBIA)
- Chemiluminescence (CIA): Bio Flash
- Electrochemiluminescence Arrays
- Nanotechnology — nanobarcodes
- Point of Care Diagnostics
  - Lateral Flow
  - Microfluidics / ‘Lab on a chip’
- Mass & NMR Spectroscopy

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implications for clinicians who are then forced to deal with apparently false negative and/or false positive results (reviewed in Fritzler38). As would be expected, there has been some resistance to accepting results from newer technologies because clinicians tend to adhere to contemporary, intuitive, clinically relevant and easily understood diagnostic paradigms. Hence, despite its disadvantages, IIF on specified substrates (i.e. HEp-2 cells) has been regarded by some as the “gold standard” for autoantibody testing in systemic autoimmune rheumatic diseases (SARD).39

The newer technologies have already informed the heterogeneity that exists within SLE cohorts and also the practicality of subsetting SLE patients on the basis of autoantibody arrays (Figure 3). In this illustration of pediatric SLE patients from the Hospital for Sick Children in Toronto, Canada, the use of serology criteria (i.e. chromatin/dsDNA, Sm/RNP, SS-A-Ro60/SSB-La; ANA negative) to subset SLE patients is possible. While there is little overlap between these serology subsets, some autoantibodies such as anti-Ro52/TRIM21 are found in virtually all serology groups. Recent evidence that anti-Ro52/TRIM21 may be a marker for “polyautoimmunity”40 in other SARD such as systemic sclerosis41 suggests that serology could be a starting point for identifying SLE subsets. Attending these shifts to newer autoantibody testing platforms is a dramatic increase in the laboratory information that is becoming available on any given patient (Figure 4). Certainly, by 2050 this may become a significant limitation unless a way is found to keep applied informatics abreast of the data sets provided by diagnostic technologies.42

It is also clear that the future will bring new understanding and evidence about the origin and functions of autoantibodies. Current views that autoantibodies are pathogenic (reviewed in Elkon and Casali43) are already being re-examined. The past half century has witnessed an arduous search for evidence that autoantibodies in SLE are pathogenic. Evidence that autoantibodies directed to double-stranded DNA participate and/or initiate lupus nephritis has waxed and waned along with fairly compelling evidence that antibodies to the protein components of chromatin are possibly more directly pathogenic (reviewed by van der Vlag and Berden44). Evidence that anti-DNA antibodies cross-reacting with N-methyl-D-aspartate receptor (NMDR) are also pathogenic and related to neuropsychiatric lupus45,46 also requires further evaluation. The list of pathogenic autoantibodies in SLE goes on, but the point is, although the

Figure 3 Heat map of autoantibody profiles in a cohort of 100 pediatric SLE patients from the Hospital for Sick Children in Toronto demonstrates remarkable heterogeneity. Intensity of reactivity with target antigens (left and right axis) are shown as red (high), orange (medium), green (low) and black (negative). Despite heterogeneity of autoantibody profiles, patients can be subclassified into four serological subsets (bottom axis): dsDNA/chromatin (35%); RNP/Sm (32%); Ro/La (14%) and Extractable nuclear antigen (ENA) negative (14%). Sera courtesy of Dr. Earl Silverman.
evidence supporting autoantibody-mediated pathogenesis of some features of SLE seems firmly substantiated, the evidence supporting the notion that all autoantibodies are pathogenic is far from compelling.

As a counterbalance to the assumptions that autoantibodies in SLE are pathogenic is rapidly growing evidence indicating that some autoantibodies protect against the onset and progression of SLE (reviewed elsewhere). This is substantiated by evidence that everyone bears their own distinctive autoantibody repertoire (reviewed elsewhere). These so-called “natural autoantibodies” are generally polyreactive, IgM isotype, low affinity and react with both self and non-self targets. Further, some of these natural autoantibodies may act as an autoimmune disease blockade by masking their antigenic targets and preventing autoreactive cells from binding the cognate self-antigens. For example, antibodies to ribonucleoprotein were thought to protect against renal disease, and the presence of rheumatoid factor in SLE was suggested to protect against the development of lupus nephritis (reviewed in Shoenfeld and Toubi). Another class of (auto)antibodies is that of catalytic antibodies or “abzymes”. The activity of catalytic antibodies is primarily localized to the variable domain of the antibody and appears to be a property of the innate diversity of the immunoglobulin repertoires. Abzymes have been described in SLE and other autoimmune diseases where defined molecular targets (i.e. target autoantigens such as chromatin) undergo hydrolysis. These and other studies suggest that autoimmunity may be abrogated by protective autoantibodies, and that eliminating or interfering with all B-cell responses (i.e. anti-CD20 and related therapies) might not be the optimal therapeutic strategy. It would seem to make sense to begin to develop therapies that selectively enhance the expression of protective autoantibodies rather than therapies that deplete them.

Last, while some SLE autoantibodies are pathogenic and others are protective, other classes of autoantibodies appear to be neutral, indifferent, and/or have roles that may not be directly traced to pathogenesis or protection. Support for these classes of autoantibodies is drawn from evidence that antibody responses to certain microorganisms have no apparent role in eliminating or targeting the offending organism. So for the time being these apparently “useless” antibodies are being relegated to “junk autoantibodies”. This notion is reminiscent of the long-held dogma that a significant proportion of the human genome consisted of “junk” DNA, only to find that a large proportion of presumed functionless (i.e. indifferent, neutral) DNA had important regulatory functions in gene expression and disease pathogenesis. By 2050, we should have a clearer picture of how all B-cell responses fit together in the larger mosaic of autoimmunity, especially in SLE.
Emerging paradigms and issues in autoantibody testing

For over half a century, testing of autoantibodies has been considered the exclusive domain of diagnostic medicine. However, in combination with other proteomic, genomic, transcriptomic and metabolomic biomarkers, autoantibodies are being recognized as providing clinically relevant information that can be applied to the rapidly emerging theme of personalized medicine (reviewed in Fritzler\textsuperscript{11}) (Table 3). Autoantibodies and their associated genomic and epigenomic markers are increasingly being used to derive meaningful subsets of patients within larger disease categories.\textsuperscript{17,60}

There is ample and growing evidence that certain autoantibodies expressed as specific isotypes or subclasses have significance in diagnostics, therapeutics and prognostics. While the importance of IgM and IgA subclasses of autoantibodies has been extensively studied, the emergence of clinical syndromes that are related to IgG4 autoantibodies and immune responses has now entered the mainstream of diagnostic medicine.\textsuperscript{61,62} IgG4, the least abundant of the IgG subclasses, is particularly interesting because it is polyvalent by exchanging half-molecules with other IgG4s, essentially recombinating random specificities in the second Fab arm for a specificity of the first Fab arm, effectively creating an IgG4 molecule with dual specificity.\textsuperscript{63} The spectrum of IgG4 autoantibodies in SLE might provide further insight into the triggers and B-cell repertoire. In addition, antibody isotypes can point to triggering pathogens. For example, in \textit{Clostridium neoformans} infections IgG2a > IgG1 > IgG2b > > > IgG3, whereas in \textit{Mycobacterium tuberculosis} IgG3 > > IgG2.\textsuperscript{55} Thus, thorough studies of autoantibody subclasses and isotypes in SLE may point to elusive trigger(s) of that disease.

Another goal should be to more thoroughly understand the efficacy of autoantibody binding to target antigens. First it needs to be appreciated that the terms protective and non-protective are relative in that they depend on a number of factors, the chief among them being the host and the “trigger” that initiated the response.\textsuperscript{55,64} Other considerations are a thorough examination of autoantibodies that bind to and activate complement components and other proteins such as integrins.\textsuperscript{54} In addition, genetic abnormalities of complement and autoantibodies directed to complement components such as C1q are also known to have significant consequences for SLE and other autoimmune diseases.\textsuperscript{65-67} Such studies can help clarify connections between adaptive immunity and pathological and/or protective autoantibodies.

While much attention has focused on the Fab idiotype of autoantibodies, the potential importance of the Fc demands some attention. It has been clearly shown that the Fc component of antibodies has a dramatic effect on the reactivity of the Fab because Fc influences the fine specificity of antibody reactivity.\textsuperscript{68,69} Of direct relevance to SLE is more recent evidence that the constant region contributes to the antigenic specificity and renal pathogenicity of murine anti-DNA antibodies.\textsuperscript{70} Hence, contemporary views that autoantibodies are simply bifunctional molecules composed of independent Fab and Fc domains is no longer tenable.

The nature of the autoantibody targets and the analytes used for SLE diagnostic immunoassays also needs to be clearly redefined. The studies of van Venrooij and his colleagues (reviewed in van Venrooij et al.\textsuperscript{71}) showing that citrullinated peptides are not only a primary target of autoantibodies in rheumatoid arthritis but are part of an immunogenetic paradigm for that disease is a pivotal discovery in the history of autoantibodies. These advances re-emphasized the importance of developing immunoassays that utilize autoantigens and analytes that are related to the disease itself. Kodadek and his colleagues at the Scripps

\textbf{Table 3} “OMICS” platforms that will augment and inform autoantibody testing

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<tr>
<th>GENOMICS/RIBONOMICS/TRANSCRIPTOMICS</th>
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<td>• Susceptibility &amp; protective genes</td>
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Abbreviations: DAMPs, danger associated molecular patterns; NETs, neutrophil extracellular traps; PAMPS, pattern associated molecular signals.
Research Institute reasoned that it is improbable that autoantibodies from a person with a given autoimmune disease would primarily bind to “normal” proteins.\(^7\) It is more intuitive that broken tolerance occurs when the immune system reacts to foreign proteins of an invading microorganism or proteins altered during cell senescence, apoptosis, necrosis or autophagy.\(^7\) Even more intriguing is the possibility that the target antigens are released from living cells as extracellular exosomes or microbodies,\(^76\) or during the formation of DNA neutrophil extracellular traps (NETs).\(^77\)–\(^80\)

These processes are all intertwined and may produce autoantibody targets that are altered by epigenetic effects, genetic mutations, microRNA dysregulation, proteasomal or exosomal dysregulation, or simply post-translational modifications (i.e. citrullination, carbamylation). These exciting developments suggest that peptoid chemistry and related approaches proposed by Kodadek, Robinson and others will be a major advancement in the field of autoimmune diagnostics and therapeutics.\(^81\)–\(^83\)

**Concluding remarks**

Our understanding of autoantibodies and their value in elucidating the etiology and pathogenesis of SLE, moving to even earlier and more accurate diagnosis, and perhaps even prevention of disease by 2050, is all part of the excitement that was generated at the SLE Congress held in Buenos Aires. Forecasting what lies ahead in 2050 is a challenge. We already live in a time of unprecedented breakthroughs in genomics, transcriptomics, proteomics, metabolomics, systems biology, and other biomedical and social sciences that are leading to better prevention, earlier and more accurate diagnosis and to innovative combinations of treatments based increasingly on each patient’s individual characteristics and preferences. Furthermore, rapid improvements in wireless and digital technologies, a rapid expansion of “apps” and other non-medical technologies contributing to prevention of disease and/or complications, and home care delivery is creating a world that is very different from the traditional medical care that we have become accustomed to. As we trace our progress to date there is certainly a sense that much has been accomplished, but also optimism that there will be remarkable and likely even unimagined advances as soon as the next SLE Congress in Vienna, Austria in 2015 and in Melbourne, Australia in 2017. Some of us will almost certainly not be around in 2050 to witness the transformations but, as amply evidenced by the speakers, poster presenters (over 400 in Buenos Aires), patients, patient advocates, and industry supporters in Buenos Aires, we have every reason to be assured that the next generation of lupus investigators is already making remarkable advances in solving the enigma of lupus, the “wolf disease”. Indeed, the butterfly from Pandora’s box is already taking wing.

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None declared.

**References**

Lupus


