Betty Diamond

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Not Dead Yet

Betty Diamond

Center of Autoimmune, Musculoskeletal and Hematopoietic Diseases, The Feinstein Institutes for Medical Research, Northwell Health, Manhasset, New York, USA;
email: bdiamond@northwell.edu

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Abstract

I have been a scientific grasshopper throughout my career, moving from question to question within the domain of lupus. This has proven to be immensely gratifying. Scientific exploration is endlessly fascinating, and succeeding in studies you care about with colleagues and trainees leads to strong and lasting bonds. Science isn't easy; being a woman in science presents challenges, but the drive to understand a disease remains strong.

THE ROCKY ROAD

Like all of us, I am a product of the family I had and the era in which I grew up. My parents had been members of the Communist Party in the late 1930s. My mother joined to end antisemitism; my father joined for economic justice. He started his professional life working with the United Auto Workers Union. In fact, he helped negotiate the first contract with equal pay for equivalent work that markedly increased salaries for women. My parents left the party in the early 1940s, and my father left the union in the mid-1940s. He went to graduate school at Harvard University, joined the faculty, and was fired during the McCarthy era for refusing to name names (1). Eventually, he was hired at Columbia University. The principles that influenced these choices stayed with my parents and informed my choices. There is no doubt that much of my activism, commitment to fairness, and willingness to buck current political or scientific fashion comes from my parents.

My father became an historian; my older brother was a history buff as a child. There was no room for me there. Neither of them was particularly interested in science, so I had some space, but also some obstacles.

From fourth grade through high school, I went to a New York City private school. It was coed through eighth grade. High school was all girls, as there weren't the science labs or the gym facilities that boys needed. I managed, however, to find ways to augment the limited math and science curriculum. I took Saturday science classes in a city-wide program for high school students and spent one summer in a program at Rockefeller University, also for high school students. The program was initiated and run by postdoctoral fellows who wanted teaching experience before moving into academic positions where they would be responsible for one or more courses. At the end of the summer, each participant was given an individual evaluation of his or her potential as a scientist. I was told I would have to choose between science or men. Thank goodness, that proved to be untrue.

I went off to Radcliffe thinking I would be a science major. My first month ended that plan. I had never been in a class of 100 or so, like the introductory chemistry and biology classes. Except for the summer at Rockefeller, I had never been in coed classes, and never in classes with premeds. I was overwhelmed by the testosterone and, not unhappily, retreated to classics and art history, but I did continue to take some biology courses. Leonard Nash, a professor of biology at Harvard and to me a wonderful man, took pity on me and told me to skip the introductory courses and take his smaller classes and tutorials, which I did. I owe another debt to Sidney Nagel, now a physicist at the University of Chicago, who held my hand through a summer school physics course I took before senior year.

At the beginning of senior year, each Radcliffe student had to meet with her dean to discuss future plans. I knew I didn't want a career in Classics; I learned that while taking my last Greek course, in which we performed close textual analyses of Homeric hymns to decide which were, in fact, written by Homer. Definitely not a career choice. And short of being chief curator at the Metropolitan Museum, I didn't see a future in art history. But I had crafted a plan. I would apply to medical school as a back door into research. Graduate schools wouldn't accept me with my limited college experience in research, but medical schools thought humanities majors made nice doctors. It was the ultimate in thinking of medicine as an art, not a science. I told my dean I was going to apply to medical school. She told me I was not a candidate and to return the following week with a more realistic plan. I consider myself both timid and stubborn. I was going to apply to medical school, but I didn't have the nerve to tell her face-to-face. I decided to call her, not to speak with her directly, which would have been unraveling, but to leave a message saying I would take my chances. I think I was fairly unraveled even by this approach, as I went into a phone booth, put the phone to one ear, and put a dime in the other.

GETTING ON TRACK

Remarkably, I was accepted to Harvard Medical School. There were some young faculty who were progressive and wanted to change the admissions process. They succeeded in getting 5 or 6 (I can't remember which) women accepted into the class of 100 my year. By two years later, women were almost 50% of the entering class. Applying to medical school was the first of many acts based on a principle I strongly believe in: Never make decisions predicated on the assumption of failure.

The medical school curriculum was perfect for me. The preclinical curriculum ended December of the second year. I was going to spend the rest of the year in a lab. Kurt Bloch had given the immunology course: five one-hour lectures that covered all knowledge of the field. The course was mesmerizing. I spoke to Baruj Benacerraf, who had just arrived at Harvard to see if I could join his lab. He told me he wasn't set up yet. I should go to Northwick Park, England, where a new clinical research program was being established under the leadership of Sir Peter Medawar. How perfect. Sadly, before I arrived there, Sir Peter had a stroke. But he came to work every day and held court at teatime, observing a Winnie-the-Pooh-like schedule, with tea at 11 AM and again at 3 PM. I worked with Stella Knight. We isolated cells from spleens, lymph nodes, and Peyer patches of mice, labeled them with or without ex vivo stimulation with mitogen, and injected them into naive mice to see their homing properties (2). Of course, at the time we didn't know about chemokines and chemokine receptors, but I loved the work and the environment. Martin Raff came by to tell us it was possible to distinguish T and B cells in blood (3). The excitement was palpable. After a year (I stayed longer than planned) I returned to Boston to complete clinical training. I was seduced by clinical medicine. I spent a few months at the then Peter Bent Brigham Hospital on the rheumatology service. I saw young women with lupus who had felt unwell for years prior to diagnosis but had been thought to be somaticizing a psychological problem. My budding feminism was piqued. My clinical training wasn't all easy. In my evaluation on the Medicine clerkship, I was told I had to smile less if I wanted to be taken seriously. Nonetheless I was committed to further clinical training.

CHOOSING A PATH

Daniel Kimberg was Chief of Medicine at Beth Israel Hospital. He had just come from Columbia. He decided I should go to Columbia for residency training, and I did. I loved my time at Columbia, although the culture was a little stiff, leading to a few encounters I hope no longer occur. For example, when I was just starting residency, I had one of those very bad, horrible, no good, rotten days with five admissions. At 2 AM I was presenting my last workup to the senior resident, who looked at the chart and noted, "At Columbia, we write lab values in red ink."

I vividly remember the day I knew it was time to return to the lab. Intravenous drug use was rampant in New York City at the time, and there were always one or two patients in the wards with hepatitis B. We did bedside rounds at Columbia. We would all stand at the bedside, two attendings, residents, and students, and one attending would ask: Should we give corticosteroids to suppress the inflammation in the liver, or should we not because the treatment might lead to unfettered viral replication? One day I thought, "I can't listen to this anymore and wait for someone else to answer the question. I need to help answer some questions, however small." When I told the Chief of Medicine that I was going to go into a lab after residency, he told me to do a fellowship first, so I would have a fallback career in case I failed at research. Again, never make decisions that assume you will fail. Paul Marks suggested some people I should talk to; Gerald Edelman didn't want me in his lab unless I came as a PhD student; Henry Kunkel terrified me. I chose to work with Matthew Scharff at the Albert Einstein College of Medicine. It is thanks to his essential goodness that he offered me a position. As I interviewed for his laboratory, he was telling me about antibody

diversity and about his efforts to model the generation of diversity in vitro, and I was working hard to understand. Matt was briefly called from the room and when he returned, I was asleep. For years he assumed I had been on call the night before. In truth, I was exhausted by my incomprehension. But I liked Matt and wanted to be back in a lab. Even though I knew I wanted to study lupus, I also knew I needed training and Matt seemed right for this.

BECOMING A SCIENTIST

I started off, like many of his postdoctoral fellows, cloning antigen-specific myeloma cells and looking for variants that no longer made an antibody that bound antigen (4). This entailed looking through a microscope at thousands of colonies cloned in soft agar in hundreds of petri dishes. The agar had to be loose to allow the cells to grow, so the clones were endlessly jiggling and I got more and more seasick. I tried Dramamine and scopolamine, and finally I told Matt I couldn't do the project. His lab at the time was also working on hybridoma technology, and Kohler and Milstein had just reported generating hybridomas from splenic B cells of immunized mice (5). Most people used this technology to make monoclonal antibodies to particular antigens, but I used monoclonal antibodies to determine effector functions of each IgG subclass (6–11). I went with Matt to an NIH (National Institutes of Health) workshop on monoclonal antibodies to report our studies. I was terrified. Not even 30 mg of valium could sooth my nerves, so Matt agreed to rehearse me one more time. My memory is we did this in the ladies' room, but that must be wrong (I haven't asked him). I slept the whole way home from Bethesda, Maryland. Matt was the perfect mentor. At least once a day he would tell me women make the best scientists. I am sure he didn't really think so, but it was very validating.

Soon after we published differences in subclass specificity and effector functions of Fc receptors, Jeff Ravetch came along and cloned the different Fc receptors (12). Obviously, knowing the structural basis for the specificity of Fc receptor binding of IgG subclasses and understanding the functional differences among IgG subclasses has been crucial to the development of monoclonal antibodies as therapeutic agents.

As the end of 3 years approached, I was looking for a job. Howard Grey invited me to interview in Denver, Colorado, at National Jewish Hospital. The auditorium was an interior room with no windows. Shortly after I began the seminar, there was a power outage. Howard asked if I would continue in the dark. I have always thought of that as a metaphor. Barry Bloom offered me a position at Einstein in the Department of Microbiology and Immunology. He had just become chair of the department, and his first two hires were Leslie Leinwand, now at the University of Colorado, Boulder, and me. I really never thought how unusual it must have been at that time to hire two women in a row, until I was writing this account. Barry chose to begin my appointment on April Fools Day, 1979. I spent over 20 years at Einstein.

It was a heady environment. Barry was studying molecules secreted by immune cells that could modulate the immune response (13). After a transformative trip to India, he began to study T cells in leprosy with Robert Modlin at UCLA (14); with Michael Brenner at Harvard University, he showed that some T cells can recognize nonprotein antigens (15). Stanley Nathenson was developing a methodology to isolate peptides from MHC class I molecules to understand T cell recognition of antigen (16). Matt was continuing to study the generation of antibody diversity. Barbara Birshtein was studying regulation of immunoglobulin gene class switch recombination (17). T.V. Rajan, like Stan, was studying T cell recognition of class I molecules (18). We six would meet Fridays for science and Chinese food, with the fortune in my cookie seeming to me like an oracle each week.

INDEPENDENCE

I knew I wanted to study systemic lupus erythematosus (SLE). My path to lupus studies was really enabled by Don Marcus, then Chief of Rheumatology at Einstein, and a glycobiologist who began all his talks by lamenting that most people can't tell a glycolipid from a hole in the ground. He suggested I attend rheumatology clinic once a week. Without his encouragement and tutelage, I never would have become a rheumatologist. Gary Solomon, a rheumatology fellow in the lab, began our efforts by generating an anti-idiotype, 3I, to anti-DNA antibodies and showing that unrelated patients made anti-DNA antibodies that had some structural or idiotypic similarity (19). We generated two other anti-idiotypes, 8.12 and F4 (20–22). Bob Schwartz made an anti-idiotype, 16/6, to anti-DNA antibodies soon after (23). He demonstrated that it bound a germ line immunoglobulin sequence. We showed that F4 bound only IgG and not IgM, suggesting to us that it might recognize an epitope acquired by somatic mutation, perhaps in the germinal center response (24). At that time, it was thought that somatic mutation occurred only in the germinal center. We had hoped to use anti-idiotypes to neutralize or eliminate at least a subset of anti-DNA antibodies, as Niels Jerne had suggested could be done in his Nobel Prize–winning model of idiotype–anti-idiotype regulatory networks (25). That never panned out.

At the that time, the views of Niels Jerne prevailed widely. For example, he argued that somatic mutation of antibody molecules eliminated autoreactivity (26). As mentioned above, Bob Schwartz at Tufts was suggesting that lupus anti-DNA antibodies were germ line encoded (27). We demonstrated that the progeny of a protective antipneumococcal antibody could acquire specificity for DNA as a consequence of somatic mutation. This study examined autoreactivity generated in vitro (28). Martin Weigert and his then MD/PhD student Mark Shlomchik studied anti-DNA antibodies generated from MRL/*lpr* lupus-prone mice and showed DNA binding arose by somatic mutation in vivo (29). We sequenced some human anti-DNA antibodies that also exhibited mutations from the germ line sequence; the mutations conferred specificity for DNA (30–32). After the sequencing of many mouse antibodies and many human antibodies, we now know that both scenarios exist. A current question in the field is, What B cell gives rise to anti-DNA antibodies in lupus? Is it a naive B cell that undergoes differentiation to a plasma cell by an extrafollicular pathway, as suggested most recently by Inaki Sanz and Jerry Boss (33, 34)? Is it a follicular B cell differentiating to a plasma cell through a germinal center pathway, as has been demonstrated in several mouse models of SLE and is suggested by the frequency and pattern of somatic mutation in many patient-derived monoclonal anti-DNA antibodies (35, 36)? We have continued to struggle with this question over the years. Recently, we developed a methodology to detect B cells reactive with nuclear antigen (ANA^+ B cells) in blood (37). This methodology is a high-throughput approach to identifying the differentiation state of ANA^+ B cells and found an increase in IgG plasma cell differentiation in SLE (37). We further found that there are two subsets of patients, one with a high frequency of ANA^+ IgM plasmablasts and a low frequency of ANA^+ memory B cells and one with few ANA^+ IgM plasmablasts and a high frequency of ANA^+ memory B cells (38). We hypothesize that the former phenotype reflects an extrafollicular pathway to plasma cells and the latter, a germinal center pathway. We are currently trying to validate this hypothesis with Nina Luning Prak through sequencing the B cell receptors of the plasmablasts from each group and looking at clonal relatedness of plasmablasts to either naive or memory ANA^+ B cells. Most importantly, this methodology allows us to isolate autoreactive B cells from blood of SLE patients and of healthy individuals and determine the frequency and pattern of mutation in B cell receptor (BCR) sequences. We can also determine whether the specificity of ANA^+ B cells in SLE patients is the same or different than in healthy individuals and determine whether progression to disease

represents a change in B cell repertoire or enhanced differentiation to IgG plasma cells of B cells that normally do not class switch (37, 39).

Early on, we wanted to know just how frequently the immune response to a bacterial antigen led to autoreactivity. This is a question that has been pursued extensively by Judith James, who has extensively studied the role of Epstein-Barr virus in SLE (40, 41). Many years before, David Stollar demonstrated cross-reactivity of anti-DNA antibodies with bacterial polysaccharide (42), and Gregg Silverman has recently hypothesized a role of gut microbiota in initiation of SLE, as anti-DNA antibodies cross-react with *Ruminococcus gnavus* found in the gut of many SLE patients (43). Based on our in vitro finding that an antipneumococcal antibody could acquire reactively with DNA, with a single–amino acid substitution, we were interested in determining whether microbial infection was routinely a trigger for the activation of autoreactive B cells in SLE as in rheumatic fever. We were making little progress generating DNA-reactive hybridomas from spleens of mice immunized with phosphorylcholine, the dominant epitope on pneumococcal cell wall polysaccharide, coupled to a protein until a very smart MD/PhD student, Subhransu (Mitu) Ray, suggested that we make a hybridoma partner that overexpressed Bcl-2. Bcl-2 had recently been shown to protect B cells from apoptosis. I wasn't in favor, as I thought that myeloma cell lines expressed high levels of Bcl-2. Just a few days later, Reuven Laskov from Israel gave a seminar showing that the myeloma line that we used for generating hybridomas had low expression of Bcl-2. I went back to the lab and told Mitu his idea was brilliant. We immunized mice with the phosphorylcholine conjugate. When we generated hybridomas from immunized mice using the Bcl-2-overexpressing fusion partner, approximately half of the B cells reacting with phosphorylcholine cross-reacted with DNA; when we used the conventional fusion partner, it was less than 5% (44, 45). This suggested that apoptosis was a mechanism for deleting autoreactivity arising in a protective immune response. It seemed reasonable that B cells that lose affinity for the triggering antigen through somatic mutation might undergo apoptosis in a germinal center response, but it was not at all clear what the fate of a cross-reactive B cell would be. That B cell would receive positive survival and differentiation signals from the microbial antigen, despite the potential pathogenicity of the antibody. The question remains unresolved. We have suggested that when a B cell leaves the geminal center and encounters self-antigen in the absence of survival factors, it first undergoes receptor editing. If this fails to remove autoreactivity, it then undergoes apoptosis (46–48). The model remains controversial.

Because lupus is a disease primarily of women, we explored the effect of hormones on B cell selection and showed that both prolactin and estrogen facilitated the survival of autoreactive B cells in a BCR transgenic mouse model. Interestingly, prolactin led to their maturation as follicular B cells, and estrogen as marginal zone B cells (49–54). Two wonderful MD/PhD students, James Cleary and Dan Michaels, performed these studies. They knew I was a football fan (I think it should be banned, but I also think it is a great game), so they gave me a then new biography of Vince Lombardi when they graduated and wrote in their inscription, "You will not find the word estrogen in this book." The role of sex hormones in B cell selection and differentiation still remains largely unexplored, but Paolo Casali has performed some elegant studies on estrogen in the germinal center response and the process of somatic mutation (55).

We have always tried to study the human disease and to use mouse models to address questions that arise in the clinic. It is clear that some patients have anti-DNA antibodies and renal disease and some have anti-DNA antibodies and no renal disease. Bevra Hahn showed that cationic antibodies preferentially deposit in the kidney, but there are some patients with cationic anti-DNA antibodies and no kidney disease (56). This led us to consider that autoantibody-mediated tissue damage requires tissue vulnerability as well as tissue-reactive antibody. Li Liao and Susan

Malkiel, PhD students, chose to address this question in a mouse model of myocarditis (57–59). They asked why streptococcal infection can induce myocarditis in DBA/2 mice but not in BALB/c mice. We immunized mice with *N*-acetylglucosamine, the epitope on the streptococcus that generates antimyosin cross-reactive antibodies. We found similar antibody titers in each strain, and indeed when antibodies from BALB/c mice were administered to DBA/2 mice, they induced myocarditis. We demonstrated that there was myosin in cardiac extracellular matrix in DBA/2 but not BALB/c mice (58, 59). It remains an issue that we know much less about organ vulnerability in autoimmune disease than about autoreactive B and T cells. Only a few risk alleles for lupus nephritis, for example, have been identified. The kidney response to the inflammatory insult in the lupus nephritis was initially studied by Shu Man Fu and colleagues (60) and more recently has been elegantly studied by George Tsokos and colleagues (61) and Joe Craft and colleagues (62).

Another MD/PhD student made an observation that opened up a whole new area of exploration in the lab and, indeed, in lupus. Jessica Katz was trying to understand the structural basis for DNA binding. She performed site-directed mutagenesis of a monoclonal anti-DNA antibody and generated a variant with tenfold higher apparent affinity for DNA (63). The parent antibody deposited in the mouse glomerulus; the variant did not. One obvious conclusion was that the parent antibody was not binding DNA in the glomerulus, as had been suggested by others. Bruce Gaynor was a medical resident who spent a year in the lab. He determined that the parental antibody bound a consensus pentapeptide sequence D/EWD/EYS/G, which we call DWEYS (64). This sequence is present in the GluN2A and GluN2B subunits of the *N*-methyl D-aspartate receptor (NMDAR). We thought we had the first potential molecular explanation for the cognitive problems that many, many lupus patients experience. Indeed, a Food and Drug Administration (FDA)-run focus group with lupus patients found that cognitive impairment is one of the three manifestations of disease that most diminish quality of life (65).

We tried transfecting a cell line with GluN2A or GluN2B and seeing if the monoclonal antibody would bind to the NMDAR. It never worked. In frustration, I brought some antibody home and asked my husband, Bruce Volpe, a neurologist and neuroscientist, to inject some of the antibody into a mouse brain. Eureka! The antibody killed neurons and I learned that the GluN2 subunits will not be expressed on the surface of a cell without coexpression of GluN1. When we transfected cells with GluN1 and either GluN2A or GluN2B, the antibody bound (66). This story has unfolded in an amazing way. Antibodies with this cross-reactivity are found in 30–40% of lupus patients and in a higher percentage of those with neuropsychiatric lupus (67). With Lonnie Wollmuth at Stony Brook University, we recently showed that they are positive allosteric modulators of the NMDAR (68). We developed a mouse model for neuropsychiatric lupus. We immunize with DWEYS peptide on a polylysine backbone so that mice develop high titers of anti-DNA, anti-NMDAR cross-reactive antibodies (69). Control mice are immunized with just the polylysine backbone. Both cohorts are given LPS to impair blood-brain barrier integrity in the hippocampus. When the "lupus" antibodies penetrate the brain, they first cause excitotoxic neuronal death, and in a second phase of pathology, we observe microglial activation and neuronal pruning (70). Uma Sriram at Temple University has shown that inhibitors of angiotensin-converting enzyme (ACE) can suppress macrophage activation (71), and several large observational studies and a few small clinical trials have shown that ACE inhibitors can retard the progression of Alzheimer disease. After showing in the mouse model that centrally acting ACE inhibitors can suppress microglial activation and lead to improvement in neuronal architecture and cognitive function, we have embarked on a clinical trial of ACE inhibitors in patients. It is an amazing feeling to move all the way from a serendipitous observation to a clinical trial. These studies were only possible because of collaborations with Bruce Volpe and Patricio Huerta, a neuroscientist who has performed the

electrophysiology and behavioral studies in mice (72); and Meggan Mackay and Cindy Aranow, two rheumatologists in clinical research, both of whom spent time in my lab; and David Eidelberg, a neuroscientist interested in dissecting brain disease through PET (positron emission tomography) technology (73, 74). I think what makes this research especially gratifying is that most lupus patients with cognitive problems or mood disorders are given anxiolytic drugs, told to see a psychiatrist, or told that their perception of cognitive compromise is fallacious. It has been unbelievably gratifying to validate their reality.

It has also been amazing to see how these studies have licensed numerous studies of the brain in murine lupus. Mike Carroll and colleagues studied the penetration of type I interferon into the brain and the ensuing activation of microglia to prune neuronal dendrites (75). Carla Cuda has also studied the brain in murine lupus, identifying the transcriptional program of activated microglia in the brain (76). Alfonzo González has revealed that antiribosomal P antibodies, associated by Keith Elkon with psychosis in SLE (77), bind a novel neuronal membrane antigen and alter neuronal function (78, 79). The proliferation of studies in mice has also spurred studies in humans. It is clear that patients without overt central nervous system (CNS) inflammation can have impairments in blood-brain barrier integrity and can exhibit evidence of microglial activation on translocator protein (TSPO) PET imaging (80). These studies have highlighted a need for therapeutic strategies for CNS disease in SLE.

Ji Lee, a very talented MD/PhD student, questioned whether maternal antibody might contribute to the learning disability identified in the children of women with lupus. She and then a postdoctoral fellow, Li Wang, showed that the DNA/NMDAR cross-reactive antibodies caused abnormal fetal brain development (81, 82). These observations led us to ask whether maternal antibodies might alter fetal brain development in other situations. Judy Van de Water had been studying the contribution of maternal antibody to autism spectrum disorder (ASD) (83). Lior Brimberg determined that brain-reactive antibodies were more frequent in women with a child with ASD than in women with a typically developing child (84). She and Simone Mader, both past doctoral fellows in the lab, identified Caspr2 as an antigen often targeted in mothers of a child with ASD (85). Exactly how these antibodies affect brain development is still unclear.

I left Einstein in 2002, as I wanted to become more involved in clinical research. For historic reasons that was not easy at Einstein. After a brief sojourn at Columbia, where I became a better scientist in large part by watching how Kathryn Calame and Steve Goff approached scientific problems, I settled at the Feinstein Institutes, the research arm of Northwell Health. At the Feinstein, I embarked on studies of the functional impact of lupus risk alleles. In collaboration with Peter Gregersen, Sun Jung Kim, first a fellow with me and now a colleague, and I showed that the *Prdm1* risk allele (encoding BLIMP-1) has diminished expression in myeloid cells and, surprisingly, not in B cells (86). The risk allele leads to enhanced activation of dendritic cells, with increased expression of cathepsin S. In mice, deletion of *pdrm1* in dendritic cells leads to a lupus phenotype in female mice only (87). Understanding how disease-associated risk alleles alter immune homeostasis opens up new pathways to using them as therapeutic targets. In lupus, we now have insights into the functional properties of several risk alleles (88–94).

C1q deficiency is the greatest genetic risk factor for lupus. Myoungsun Son in my lab, following a suggestion from Frances Santiago-Shwartz, demonstrated that C1q binds LAIR1, an inhibitory receptor on immune cells (95–97). She and Tianyi Liu went on to show that activation of macrophages by HMGB1, a damage-associated molecular pattern (DAMP), polarizes the cells to an M1-like phenotype with release of inflammatory cytokines and leukotrienes (98). If macrophages are exposed to both HMGB1 and C1q, they polarize to an M2-like phenotype with secretion of IL-10; high expression of mer-tk, a receptor tyrosine kinase that is involved in phagocytosis; and secretion of resolvins. This requires binding of C1q to LAIR1. Since our initial

identification of LAIR1 as an inhibitory receptor, LAIR1 has become a hot area of research. It is now a therapeutic target in cancer clinical trials (99), and high expression of LAIR1 on blood monocytes correlates with poor outcomes in individuals with COVID-19 (100).

FORAYS INTO CLINICAL TRIALS

As I focused more on clinical research, I also became involved in clinical trials. I have been a member of the Immune Tolerance Network (ITN) since its inception. I saw Jeff Bluestone annually at the FASEB Summer Research Conference on Autoimmunity at Saxtons River, Vermont. He had successfully competed for the NIH program to merge clinical trials to mechanistic studies in autoimmunity, transplantation, and allergy to understand pathways to both success and failure. The ITN was soliciting suggestions for clinical trials, and I asked many in the lupus community what trial they most wanted to see performed. David Wofsy had performed critical studies of costimulatory blockade in mouse models of lupus (101). CLTA4-Ig was available for use in humans, and he and I with numerous colleagues undertook a trial of CLTA4-Ig in patients. I learned an amazing amount from him. Most importantly, I learned that designing a clinical trial is hard. The trial failed, and I learned that learning from failure is also hard. We did learn that one could decrease prednisone to 10 mg in essentially all patients over an eight-week period (102). This is now standard in clinical trials for SLE. We next spearheaded a clinical trial of B cell depletion with rituximab followed by BAFF inhibition with belimumab in SLE, also without clinical efficacy but proving that BAFF blockade diminished the maturation of autoreactive B cells from the transitional to the naive stage, as had been shown in mice (103).

Adhering to the principle that it is generally best to say yes (I believe that in child raising also), David and I also became involved in the Accelerating Medicines Partnership in SLE, along with Arnon Arazi, Nir Hacohen, Soumya Raychaudhuri, Anne Davidson, and many others. Dissecting the heterogeneity of lupus nephritis by performing single-cell RNA-seq of all cell types in the kidney has been, and continues to be, a monumental task (104). One of the most important outcomes may be to learn which mouse models of lupus most mimic the human disease. This will help identify the mouse models that should be used to explore new therapeutics.

BEYOND THE LAB

Besides research, I have always enjoyed building programs. I was still an Assistant Professor when I assumed the leadership of the MD/PhD program at Einstein. I am intrigued, even obsessed, with how you design a program to prepare students to be productive scientists in 30 or 40 years' time. But mainly I love interacting with the students, watching their scientific growth, enjoying their antics, and helping them (hopefully) confront professional challenges. I now run the MD/PhD program at the Zucker School of Medicine at Hofstra/Northwell. Over all these years, there has been no diminution in my commitment to and enjoyment of the students. There is truly no better job in a medical school.

I have also served as Chief of Rheumatology at Einstein and then at Columbia. I became Division Chief reluctantly, only when it was clear that if there were to be a flourishing research program in rheumatology, someone would need to recruit additional scientists. I am proud of the research groups I established at Einstein and then again at the Feinstein as chief of a section on autoimmunity.

Over the years, I have been involved in numerous activities. I believe I have learned from participating in all of them. The appeal of a new experience always won out over exclusive attention to ongoing research. For example, I was on a panel empowered by the Federal Judiciary

to consider the potential impact of silicone breast implants on development of autoimmune disease (105). I joined the panel (this is now over 20 years ago) because just before I received the invitation, a friend had a dream. In her dream, she asked my husband and me to travel with her. I said, "I can't, I'm writing a grant." She spluttered "Betty you're 75 years old [actually, I'm still not there] and still writing grants!" The dream made me feel I needed to understand professional alternatives, so I accepted the invitation. The work was hard but fascinating, and the stakes high. On one side, there was what seemed to be the best interpretation of data, that there was no compelling causal relationship; on the other side, there were cultural issues of female patients who were victims of doctors—unscrupulous at worst, uninformed at best. These women were not informed that over time the surgery would likely lead to disfigurement, as so many implants would leak. The intersection of science and society has become even more important over the pandemic years.

Service to the scientific community has always been important to me. I served as president of the American Association of Immunologists (AAI) and was pleased that the annual meeting the year of my presidency was held in Baltimore, home to Stringer Bell, who had a dream, and Avon Barksdale and Omar Little, gentlemen who had a code of conduct. I served on the Scientific Council of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the NIAMS Board of Scientific Counselors (I almost was not allowed on these committees when a background check revealed that I had been a member of Students for a Democratic Society). I served on the Board of Directors of the American College of Rheumatology (ACR). At my first ACR directors' meeting I noted a lack of diversity and suggested that the organization needed to update. I was asked to chair a task force to consider the issue. It was a great group. We sought to understand why, beyond social justice, diversity might be important. I learned, as I learned over and over again, that whenever you seek information on a topic on which you know little, you find many smart people have been thinking about it for years. We issued our report and I rotated off the board. The following year at the annual meeting I was the sole woman asked to speak in the basic science review session. The moral of the story: Don't expect rapid change. I came back from the meeting, however, determined to start an organization of women scientists at the Feinstein to promote our professional advancement and enjoyment. I proposed its name: Advancing Women in Science and Medicine, or AWSM, pronounced awesome. It was amazing to me how empowering it was just to collectively acknowledge a problem and agree to help each other grow professionally.

THE PRESENT

So where do I stand now? There is much more I want to accomplish as a scientist. So many more questions. So much need for those with SLE. But looking back, I am proud of my trainees. I truly believe that growing scientific progeny is as important as one's scientific accomplishments. And I am proud of being an advocate for women and marginalized individuals in science. The microaggressions are real and grow more exhausting over time; there need to be voices to counter these and support those who suffer from stereotype threat, just as Matt Scharff supported me. All in all, though, I continually marvel that I get paid for what I do, as it is such a gift to be a physician-scientist.

But I cannot end without a plea. With perhaps some rare exceptions, what we do as citizens is as important as what we do as scientists. Engage to affirm the value of evidence-based decision making and the importance of ensuring that we embrace a diverse scientific workforce and that all individuals benefit from biomedical advances. That alone will not ensure a better world, but it will help.

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