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## Review

# From defining antigens to new therapies in multiple sclerosis: Honoring the contributions of Ruth Arnon and Michael Sela

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## ABSTRACT

Ruth Arnon and Michael Sela profoundly influenced the development of a model system to test new therapies in multiple sclerosis (MS). Their application of the animal model, known as experimental autoimmune encephalomyelitis (EAE), for the discovery of Copaxone, opened a new path for testing of drug candidates in MS. By measuring clinical, pathologic, and immunologic outcomes, the biological implications of new drugs could be elucidated. Using EAE they established the efficacy of Copaxone as a therapy for preventing and reducing paralysis and inflammation in the central nervous system without massive immune suppression. This had a huge impact on the field of drug discovery for MS. Much like the use of parabiosis to discover soluble factors associated with obesity, or the replica plating system to probe antibiotic resistance in bacteria, the pioneering research on Copaxone using the EAE model, paved the way for the discovery of other therapeutics in MS, including Natalizumab and Fingolimod. Future applications of this approach may well elucidate novel therapies for the neurodegenerative phase of multiple sclerosis associated with disease progression.

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## 1. Introduction

Ruth Arnon was born in 1933 in Tel-Aviv. Her mother, a teacher, was born in Jaffa, and belonged to one of the families of early pioneers that arrived in Palestine in 1882. Her father, who came to Palestine from Russia at the age of six, was one of the first electrical engineers at the Palestine Electric Company that had just been established. Her entire education was in Israel – elementary and high school in Tel-Aviv, followed by University studies at the Hebrew University in Jerusalem. As a member of the ROTC, after graduating her M.Sc. degree in Biochemistry she was drafted into the IDF as an officer in the Navy, serving as a chemist in the Naval Laboratory. Upon her release in 1956 she joined the Weizmann Institute of Science as a Ph.D. student, initially with Efraim Katchalsky (later Katzir) and at a later stage under the supervision of Michael Sela. Her Ph.D. thesis, entitled “The Chemical Basis of Antigenicity of Proteins” served as a cornerstone in the budding field of immunochemistry. In this work she studied systematically the effect of attaching short polypeptide chains of individual amino

acids on the immunogenicity of gelatin (a protein considered non-immunogenic at the time). The amino acid with the highest effect was tyrosine, a certain amount of which also converted the specificity of the protein to that of the tyrosine chains. This effect was intensified by the inclusion of glutamic acid. This project culminated in the preparation of the first synthetic antigen – a multi-chain polymer denoted (TG-A–L), and led eventually to the development of the entire field of synthetic antigens that enabled a better understanding of various phenomena in immunology.

After graduating, she underwent post-doctoral training with Gertrude Perlman at the Rockefeller Institute. Her study focused on the antigenic properties of enzymes such as pepsin and pepsinogen, and the relationship between immunological and enzymatic properties to structural modification. These pioneering studies, which she then expanded to other enzymes such as papain and chymopapain, trypsin and chymotrypsin, as well as lysozyme, opened the entire field of immunochemistry of enzymes, which she used as a model for biologically active molecules. Her studies on the lysozyme “loop” resulted in the first synthetic antigens with antiviral activity: After demonstrating that immunization with synthetic peptides analogous to fragments of enzymes or bacterial toxins inactivates their biological effects, she showed that the same principle holds for a fragment of a viral (the MS-2 bacteriophage) protein, antibodies against which neutralized the virus. On this

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basis she built a most original approach for designing innovative vaccines – namely, synthetic epitope-based vaccines, leading to the development of a universal influenza vaccine, which is at present in Phase II clinical trials.

Her most significant achievement which is directly related to autoimmunity is the development of a synthetic vaccine/drug against multiple sclerosis (MS), denoted Copolymer 1, which was carried out in collaboration with Michael Sela and Dvora Teitelbaum. This compound which was designed to simulate the major myelin component Myelin Basic Protein, was shown to suppress very efficiently the animal model of MS in several species, including primates. Its beneficial effect in MS patients, with an excellent safety profile, was demonstrated in a double-blind clinical trial, performed by Murray Bornstein. As a result, Copolymer 1, also known as glatiramer acetate (GA) and COPAXONE®, was approved for the treatment of MS and is presently used by over 200,000 patients worldwide. In parallel to the drug development, she focused on elucidating its mechanism of action, and demonstrated that in addition of its immunomodulating effect, it also induces neuroprotection, neurogeneration as well as remyelination Fig. 1.

During her more than 50 years of scientific career she was awarded many prizes and honors including the Robert Koch Prize in Medical Sciences, Spain's Jimenez Diaz Memorial Award, France's Legion of Honor, the Hadassah World Organization's Women of Distinction Award, the Wolf Prize for Medicine, the Rothschild Prize for Biology, the AESKU Prize for Life Contribution to Autoimmunity and the Israel Prize for Medicine. She received Honorary Degrees from Tel-Hai College; Ben-Gurion University of the Negev, Tel-Aviv University, and The Open University of Israel.

Her entire career was at the Weizmann Institute where she served as Head of the Department of Chemical Immunology, Dean of the Faculty of Biology, as well as Senior Vice-President. She has also spent periods abroad, at the University of Washington in Seattle (with Hans Neurath), at UCLA (with John Fahey), at Institut Pasteur (with Louis Chedide), at Walter and Eliza Hall Institute in Melbourne (with Gus Nossal) and at the ICRF in London (with Walter Bodmer), as well as at the NIH as a Fogarty scholar. On an

international level – she served as the President of EFIS (European Federation of Immunological Societies) and as the Secretary-General of IUIS (International Union of Immunological Societies). She is a member of the Israel Academy of Sciences and Humanities. She is also an elected member of EMBO and of the American Philosophical Society. She was the President of the AASA (Association of Academies of Sciences in Asia). She is presently the President of the Israel Academy of Sciences and Humanities.

Michael Sela was born in 1924 in Poland, moved with his family to Bucharest (Romania) in 1935 and succeeded in reaching Eretz-Israel in February 1941. He studied at the Hebrew University on Mount Scopus in Jerusalem and received his M.Sc. in 1946. He started studying for Ph.D. in the University of Geneva, but interrupted it during the war of independence, which resulted in the Declaration of Independence of Israel. He spent an additional couple of years in Italy and as Commercial Secretary in the Legation of Israel in Prague (Czechoslovakia). He returned to Israel in August 1950 and started immediately working at the Weizmann Institute of Science as a Ph.D. student of Efraim Katchalski (later Katzir). Ph.D. granted in 1954. At the beginning he was involved in studies on the synthesis and characterization of polymers of amino acids, including polytyrosine. By using polylysine or proteins as initiators of polymerization, he was the first to build multichain polymers of amino acids and polypeptidyl proteins. By building polytyrosyl gelatin he inquired whether it is immunogenic (by the way he introduced in the immunological literature the notions of immunogen and immunogenicity), and found that, depending on the amount of tyrosine residues attached, the antibodies were either specific for tyrosine peptides or for gelatin. This turned to the formation of synthetic polypeptide antigens, with whose help it was possible to define the molecular basis of antigenicity.

Moving to NIH, Michael Sela began to work with Chris Anfinsen and co-discovered that the sequence of protein defines its structure, and there is no need for additional genetic information to tell it how to fold. For many years later he combined his interest in immunology and protein chemistry. In collaboration with Hugh McDewitt he discovered the genetic control of immune response,



Fig. 1. L to R: Murray Bornstein, Ruth Arnon, Michael Sela, kindly provided by Ruth Arnon.

thanks to the use of single antigens – polymers of amino acids – where one could prepare them precisely. Moving to autoimmunity, he invented with Ruth Arnon a drug against multiple sclerosis, and with Edna Mozes a candidate drug against myasthenia gravis. In parallel, he investigated for many years until today the immunological approach to fight cancer. He was the first to discover the synergistic effect of an antibody and a chemotherapeutic drug in fighting cancer. Last year he published his studies using a synergistic approach to pancreatic cancer and to triple-negative breast cancer. Most recently he published a study showing the possibility that aptamers might replace antibodies in treating diseases.

During his 63 years of research he was awarded many prizes and honors. He became a member of 17 academies of science, including Israel Academy of Science and Humanities, National Academy of Sciences of United States, Pontifical Academy of Science (in Vatican), Leopoldina, American Academy of Arts and Science, Romanian Academy, Russian Academy of Science, American Philosophical Society, French Academy of Science, Accademia Nazionale dei Lincei (Italian), Polish Academy of Arts and Sciences and European Academy of Sciences and Arts. His prizes include in 1959 Israel Prize in Natural Sciences (at the age of 35), Otto Warburg Medal of the German Society of Biological Chemistry, Rothschild Prize in Chemistry, von Behring Prize (Germany), Gairdner Foundation International Award (Canada), Prize of the Institute de La Vie (France), Prez lauber (Geneva), UNESO Albert Einstein Golden Medal, Adolf von Harnack Medal of the Max-Planck-Gesellschaft, Interbrew-Baillet Latour Health Prize (Belgium), Wolf Prize in Medicine (Israel).

His honorary Fellowships include American Society of Biological Chemists, Harvey Society, American Association of Immunologists, Scandinavian, French, Colombian, German and Romanian Societies of Immunology. His honorary doctorates are from the National Autonomous University of Mexico, from Université de Bordeaux, Tufts University (Mass), Colby College (Maine), University Louis Pasteur in Strasbourg, Hebrew University (Jerusalem), University of Tel-Aviv, Ben-Gurion University of the Negev, as well as honors from the Open University of Israel and the College of Management Academic Studies, in Rishon LeZion. He was made an Officer, and later Commander of the Legion d'Honneur, France, Commander of the Order of Merit Award of the Federal Republic of Germany, Great Officer of the Italian solidarity Star, Caballero, Order de San Carlos, Colombia. He is a Foreign member of the Max Planck Society (Institute of Immunology and Epigenetics in Freiburg). He has been for tens of years adviser to WHO and ran for 25 years a laboratory course in immunology for WHO and UNESCO. He is one of the founders of EMBO, and served as the fourth President of its Council. After EMBL was created he served as its first President of its Scientific Council.

He spent periods abroad at NIH (three times for more than a year), Bloomington (Indiana), College de France, Institut Pasteur, Berkeley, Harvard, MIT, Tufts Medical School. He is a honorary citizen of New Orleans and of Rehovot. Being involved in arts and music, he is Honorary President of Bat Sheva Dancing Company, and is actively involved in Artur Rubinstein Master Piano Competition.

Between 1975 and 1985 he served as the President of the Weizmann Institute of Science, and since then he become an Institute Professor.

In 1972, the senior author of this introduction took note of a paper from the Weizmann Institute, written by Dvora Teitelbaum, Asher Meshorer, Tsvi Hirshfeld, Ruth Arnon and Michael Sela [1]. He corresponded with Michael Sela, and visited him in the summer of 1972 in his office at the Weizmann. Michael was gracious and gave him more than an hour of his time, where he outlined the work on synthetic chemistry that was ongoing in his department, named Chemical Immunology. He chose to do a post-doctoral fellowship with him, as he headed to a career combining

neurology and translational immunology. After completing internship at Stanford, he arrived at the Weizmann at the end of 1974. He was assigned a bench on the ground floor in the Wolfson Building at the Weizmann in the laboratory where Dvora Teitelbaum and Cynthia Webb were working on a synthetic polypeptide called Cop-1, under the supervision of Ruth Arnon and Michael Sela.

He was drawn to Stanford and the Weizmann Institute because of an earlier experience in 1967 working on a new field called the genetic control of the immune response. His first research experience at Salk Institute, under Ed Lennox, involved injecting different inbred strains of mice with influenza virus, to look for a differential response. A few years earlier Sela and McDevitt had shown that a linear branched chained polymer comprised of tyrosine, glutamate, alanine and lysine, abbreviated (T,G)-A-L elicited an immune response under genetic control [2]. McDevitt mapped the genes controlling the genetic control of the immune response to the major histocompatibility complex [3].

Copolymer 1 was initially developed as a potential method for inducing experimental autoimmune encephalomyelitis without having to visit the abattoir to obtain a cow's spinal cord, in order to purify myelin basic protein. Building on the successes with the ordered linear polypeptide (T,G)-A-L, Sela, Arnon and Teitelbaum took these four amino acids in the same relative molar concentration as they occurred in myelin basic protein, and synthesized a random copolymer. They hoped that this random copolymer would have some of the structures contained in myelin basic protein and that it would induce disease. Attempts to induce EAE failed, but the copolymer was effective in preventing and reversing EAE [1,4].

The ability to modulate clinical, histological and immunological facets of EAE was one of the major contributions of the initial discovery efforts leading to Glatiramer acetate [1]. Teitelbaum and colleagues wrote, "The use of a synthetic copolymer described here is advantageous over these two methods, since the polymer is devoid of encephalitogenic activity and is not immunosuppressive. "In 1972 in a follow up paper in Nature [5], Teitelbaum, Webb, Meshorer, Arnon and Sela, emphasized that although myelin basic protein itself could be used to prevent EAE, when given in large doses in incomplete Freund's adjuvant [6], that the newly discovered copolymer was superior in concept, because it was unable to induce EAE. The use of a potentially autoimmune inducing myelin protein, was clearly potentially dangerous in comparison. As Teitelbaum and colleagues wrote in Nature, "... it protects the animals efficiently from high dose of the encephalitogenic protein, which would have otherwise induce the disease in most animals" [5].

EAE was first described in the 1930's at the Rockefeller Institute, while studying complications of immunizations that sometimes result in acute disseminated encephalomyelitis [7]. These reports from Arnon and Sela's group at the Weizmann, on the heels of Kies and her colleagues application of this model a decade earlier [6], helped to establish EAE as a durable template for testing potential therapies for multiple sclerosis. In many ways EAE has served the field of MS research [8], just as replica plating and bacterial culture on drug coated disks has served the field of resistance to antibiotics [9], or parabiosis experiments paved the way for the cloning of leptin. The Lasker committee lauded Coleman who shared the prize with Friedman for his use of 'connected circulatory systems' parabiosis in the breakthrough discovery: "To investigate further, he turned to another overweight mouse, this one called "obese", whose aberrant physiology arises from two defective copies of a different gene (*ob*). Although the "obese" and "diabetes" mice displayed almost identical features—heft and other metabolic irregularities—they behaved radically differently after Coleman connected their circulatory systems. Nothing happened to the

“diabetes” animals, but the “obese” mice starved to death, just as the normal rodents had in the previous experiment. In contrast, attaching normal mice to “obese” animals did not perturb the normal creatures and caused the “obese” ones to trim food consumption and gain less weight than usual” [10].

## 2. Persistence and patience in application in the clinic

From the early pre-clinical experiments in 1971 to the approval of glatiramer acetate (Copaxone) in the US in 1996, was a saga that occupied a quarter century. Murray Bornstein directed the first clinical trial published in 1987 showed a remarkable reduction in relapse frequency [11]. The details of this saga have been reviewed extensively [4]. Since approval in 1996, glatiramer became the most widely prescribed drug for relapsing remitting MS to date.

## 3. The EAE template for drug development in MS: A notable success and one big failure

*The Notable Success:* The development of Natalizumab, the most potent approved drug for treatment of relapsing remitting MS, depended on a critical application of the EAE model. In 1990 in collaboration with Ted Yednock at Athena Neurosciences, later acquired by Elan Pharmaceuticals, we sought to characterize the key molecules involved in lymphocyte homing to brain. We used the EAE model in the manner that had been ‘passed down’ to me as a student of Ruth Arnon and Michael Sela. First we used an existing assay, the Stamfer Woodruff frozen section binding assay. In late 1980s most studies with this assay were done on lymphoid tissue, particularly in the study of high endothelial venules [12,13]. Here we adapted the assay to test the binding of monocytes to inflamed brain endothelium in EAE. We analyzed monocyte binding to endothelium and attempted to inhibit the interaction with various antibodies to cell adhesion molecules including various monoclonal antibodies to  $\alpha 3$ , 4, 5, and 6 integrin; to  $\beta 1$  and 2 integrin; to LFA-1 (CD18 and CD11a) and Mac-1 (CD18 and CD11b); to I-selectin; to CD2, CD4, and CD45; to OX44; and to Thy 1.1 [14,15].

The EAE experiment provided an exciting outcome: “Remarkably, lymphocyte attachment to the lumen of inflamed vessels was almost entirely blocked by antibodies to 1 integrin. The integrin molecule's chain binds to 1 of 6 unique chains. Antibodies specific for the chains were applied to the frozen section assay; an antibody to  $\alpha 4$  integrin inhibited lymphocyte binding to the frozen brain sections. Thus, binding was inhibited with antibodies to  $\alpha 4$  or to  $\beta 1$  integrin. Surprisingly, other integrins and I-selectin had no effect on binding to inflamed brain endothelium” [14,15]. The second part of

the EAE experiment looked at the effect of an antibody to  $\alpha 4$  integrin on EAE induced with cloned T cells that induced paralysis [15]. “We administered the 4 integrin antibody 2 d after injection of the highly pathogenic clones, which can home to the brain within 4–12 h. Remarkably, treatment with this antibody prevented paralysis in 75% of animals. Even in those animals with paralysis, the signs were weaker and appeared later than those who received a control antibody. Thus, importantly, we could have a clinical impact long after some cells had reached the brain. We found that the 4 integrin antibody blocked the appearance of inflammatory cells in the brain” [14]. We concluded audaciously, perhaps, “that therapy based on inhibiting  $\alpha 4 \beta 1$  integrin may prove effective in treating inflammatory diseases of the central nervous system” [15].

Clinical trials over the next 10 years showed that a humanized antibody to  $\alpha 4$  integrin Fig. 2 reduced the relapse rate in relapsing remitting MS by 70%. In 2004 Natalizumab was approved by the FDA. It is recognized as the most potent approved drug to treat MS. The drug has an Achilles heel. One in 500 patients develop progressive multifocal leukoencephalopathy (PML) after more than 2 years of monthly injections of Natalizumab. A blood test based on levels of antibodies to the John Cunningham (JC) Virus that triggers PML is approved for mitigation of risk to PML. Approximately 50% of patients are negative for JC virus, and these patients have essentially no risk of developing PML [16–19] (Table 1).

An adaptation of the EAE model in this case allowed us to show the pre-clinical proof of concept that initiated clinical trials on Natalizumab. The formula used by Ruth Arnon and Michael Sela to develop Copaxone, again paid dividends with the development of Natalizumab.

*The Problematic Failure:* Arnon and Sela described three key specifications underlying the use of EAE for the development of a version of antigen specific therapy for MS [4,5]: First, one should not only prevent disease, but the therapy should reverse ongoing disease after antigen spreading has occurred. Second, the putative therapeutic should not be pathogenic, that is the putative drug should not induce EAE in pre-clinical studies, nor worsen MS when tested in humans. Third, the potential therapy should modulate the immune system, especially in terms of down-regulating pathogenic cytokines. In the age of Th1/Th2 the third requirement aimed at reducing Th1 and enhancing Th2. Now we might want a therapeutic that would down-regulate Th1 and Th17, while inducing regulatory T cells in an ideal scenario. In the early 1990s, the altered peptide ligand was such an ideal approach that might meet the three required specifications.

In 1994 we showed that an altered peptide ligand of the immunodominant determinant of myelin basic protein could

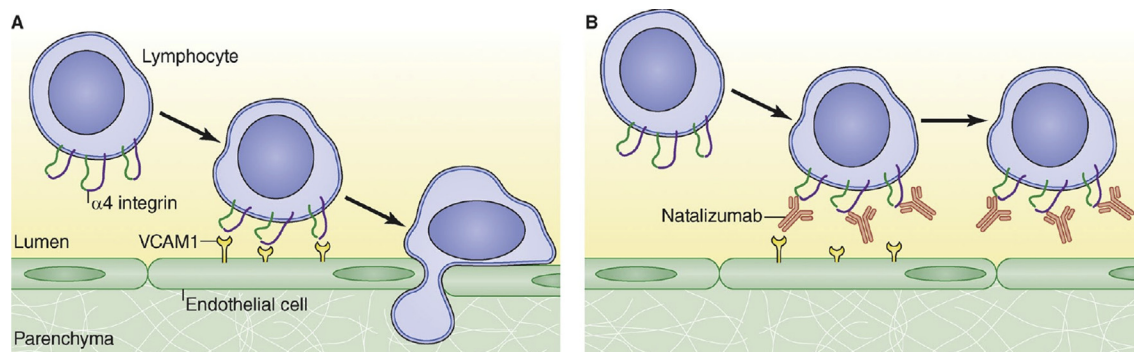


**Fig. 2.** Legend: Natalizumab blocks lymphocyte homing in MS. (A) 4 integrin binds to vascular cell adhesion molecule 1 (VCAM1) and to osteopontin (not depicted) on inflamed brain endothelium. This interaction gives lymphocytes access to the central nervous system (CNS). The presence of immune cells in the brain is a prominent feature of MS. (B) Natalizumab, a humanized antibody to  $\alpha 4$  integrin, blocks binding of lymphocytes to VCAM and osteopontin on inflamed brain endothelium, thereby preventing lymphocyte entry into the CNS. With permission of author.

**Table 1**  
Estimated US incidence of PML stratified by risk factor.

| Anti-JCV antibody negative <sup>b</sup> | Natalizumab exposure <sup>c</sup> | Anti-JCV antibody positive <sup>a</sup> |                             |
|-----------------------------------------|-----------------------------------|-----------------------------------------|-----------------------------|
|                                         |                                   | No prior immunosuppressant use          | Prior immunosuppressant use |
| <1/1000                                 | 1–24 months                       | <1/1000                                 | 1/1000                      |
|                                         | 25–48 months                      | 3/1000                                  | 13/1000                     |
|                                         | 49–72 months                      | 7/1000                                  | 9/1000                      |

The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%.

<sup>a</sup> Based on US post-marketing PML data as of September 3, 2013 and natalizumab use data as of August 31, 2013.

<sup>b</sup> Calculations based on 2 cases of anti-JCV antibody negative PML in patients exposed for at least 1 month of therapy as of September 3, 2013. Data for anti-JCV antibody negative patients reflects worldwide exposure.

<sup>c</sup> Data beyond 6 years of treatment are limited.

Source: Tysabri (natalizumab) [package insert].

reverse paralysis in EAE. Moreover, Th1 responses to myelin were reduced [20]. In 1996 we showed that this reversal of clinical EAE, drastically and rapidly reduced inflammatory infiltrates [21]. The reversal of disease depended on the Th2 cytokine, IL-4, as an anti-IL-4 antibody reversed the therapeutic benefit [21]. Based on these studies clinical trials in relapsing remitting MS were undertaken in a multicenter trial with an APL to myelin basic protein. A smaller trial was run at the NIH with the same APL.

The two studies produced seemingly contradictory results. When tested at three doses the altered peptide induced a fall in activity, as measured by gadolinium enhanced lesions on magnetic resonance imaging [22]. A vigorous Th2 response with alarming allergic reactions, particularly at the highest dose, lead to the premature termination of the Phase 2 trial [22]. Apparently too much Th2 responsiveness was an intolerable side effect. We ultimately learned that anaphylaxis to self-antigens including myelin proteins was possible after self-tolerance was broken. Antigens that were expressed in thymus, where central tolerance occurs, were less likely to induce anaphylactic responses [23]. These studies emphasized that a simple Th1 to Th2 shift, was problematic in itself.

When the same drug was tested at the highest dose in a small group of patients at NIH in an open label study, there was evidence of worsening in some patients. Analysis of the T cell response to myelin basic protein indicated that at least in some patients there was activation of the T cells [24]. Writing in a News and Views, Genain and Zamvil asked, “Are the findings of the two studies contradictory? The number of patients enrolled in the study of Bielekova et al. was small, and the study was ‘unblinded’ and not placebo-controlled, thus it is difficult to evaluate the frequency at which the reported complication would occur in a larger, ‘blinded’ trial. In contrast, the study of Kappos et al. [22] involved many more patients distributed throughout several international centers.

Kappos et al. [22] undertook a ‘double-blind’, placebo-controlled study involving 142 patients, and tested three different doses of the APL (5 mg, 20 mg and 50 mg in weekly subcutaneous injections). The authors did not find any differences in the relapse rate between APL- or placebo-treated patients, but report that the volume and number of enhancing lesions were reduced in patients receiving the lowest APL dosage. They found that treatment with APL induced a TH2 response against MBP in a subgroup of patients. Although a worsening of the clinical course was not found, this trial was terminated because of a high incidence of immediate-type hypersensitivity reactions, which occurred mostly at the 50-mg dose.

The study by Bielekova et al. [23,24] which included eight patients, tested only the 50-mg APL dose. The authors report that APL

treatment led to a higher incidence of MS exacerbations in three patients. Their sophisticated immunologic analysis shows that T-cell populations specific for APL and MBP<sub>83–99</sub> expanded in these patients. Many of these MBP-specific T cells had a TH1 pro-inflammatory phenotype and were found in the peripheral blood. However, the authors do not provide direct evidence that the APL treatment triggered the exacerbations, although the data from one patient (MS 502) seem compelling. Despite the lack of causal relationship, this trial was also terminated.”

“Accumulating evidence indicates that there is great flexibility in T-lymphocyte recognition of antigen sequences, which implies that multiple determinants, including foreign and viral peptides, may activate autoimmune responses. Presentation of different antigenic peptides to the TCR complex can activate different T-cell signaling pathways (such as differential phosphorylation of the CD3 invariant chain), leading to different T-cell functions.”

Clearly EAE though highly successful in helping to initiate the development of Copaxone and Tysabri, was problematic when altered peptide ligands were developed in the clinical. Unexpectedly we learned that it was possible to have allergic responses to self, and that an altered peptide ligand for most individuals might lead to a superagonist response in others. The term ‘experimental’ in EAE must be emphasized. Not all experiments are ‘successes’, and even the negative experiments may illuminate fascinating biologic mechanisms, such as ‘allergy to self’ [23].

#### 4. Final comments

Ruth Arnon and Michael Sela have had a major impact on the careers of many scientists. In particular, in the case of Larry Steinman, he has attempted to repeat their prescient use of the EAE model for the development of therapy for MS and other autoimmune diseases. While this tactic proved successful with Tysabri [14], the experience with altered peptide ligands was chastening [22–25]. One quality that shines through from their experiences with the development of Copaxone is the need for resilience and persistence: The development of Copaxone took more than a quarter of a century from bench to bedside. Immunologists become humbled in their attempts to treat autoimmunity. Often such diseases defy all logic. A recent PubMed search using the terms “treatment and autoimmunity”, had over 10,000 hits, with therapies that range from monoclonal antibodies to drug-induced immunomodulation, use of microbiota transfer, immunosuppression, alterations by cytokines, chemokines, and/or their cognate receptors, stem cell replacements, altered peptide ligands, blocking antibodies, idiotype or anti-idiotype therapy, modulation of apoptosis, DNA vaccination, total lymphoid irradiation, subpopulation replacement and/or deletion and gene therapy [26–68].

The ‘long and winding road’ is a good metaphor, and one must be patient when translating from the bench to the patient! In the meantime we are diligently pursuing new therapies for attaining antigen specific tolerance in diseases like neuromyelitis optica and type 1 diabetes [69–72]. The style and brilliance of Arnon and Sela serve as beacons on this path.

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