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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.

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 multichain polymer denoted (T,G-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 McDevitt he discovered the genetic control of immune response,

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