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Michael Sela: Scientist, statesman, sage (1924–2022)

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Michael Sela died May 27, 2022, at the age of 98. A synthetic chemist, his discoveries contributed fundamentally to our understanding of the genetic control of the immune response and the development of breakthrough therapeutics for multiple sclerosis (MS) and cancer. His impact on the world of science went far beyond his own scientific discoveries. At the same time, while caring deeply and conscientiously as a scientific mentor, Michael soared in various positions as a true "statesman of science." His academic career spanned more than 70 years at the Weizmann Institute of Science in Rehovot, Israel, and early on two of his role models were chemists and statesmen who became presidents of Israel, including Israel's first president, Chaim Weizmann, who was an organic chemist, and his doctoral adviser, biophysical chemist Ephraim Katzir, the fourth President of the State of Israel. The Daniel Sieff Research Institute was renamed the Weizmann Institute in 1949.

Miechzslaw Salomoniwicz was born in Poland on Feburary 28, 1924. Like many Eastern European Jews, he chose a Hebrew name when moving to Israel. His father owned a textile factory. As the global economy slumped, the family moved to Romania in 1935. With antisemitism on the rise, the family decided to move to Israel. At the age of 17, Michael left Romania and set out by himself to join his family, taking a boat across the Black Sea to Turkey, then a train to Lebanon. The British admitted him to Mandatory Palestine, where he was reunited with his family, who arrived a week later (1).

Michael studied at the Hebrew University on Mount Scopus in Jerusalem and received his Masters of Science in 1946 (1). Michael intended to begin doctoral studies in Geneva but moved to Italy, where he helped in the resorption of Holocaust survivors. During this period, he later served as Commercial Secretary in the Legation of Israel in Prague, Czechoslovakia. Michael returned to Israel in August 1950 and began his studies in chemistry at the Weizmann Institute of Science as a doctoral student of Efraim Katchalski, later Katzir (2).

Early in his career, Michael was involved in studies on the synthesis and characterization of polymers of amino acids, including poly-tyrosine. By using poly-lysine to initiate polymerization, he was among the first chemists to build multichain polymers of amino acids and polypeptide proteins. With these synthesized polymers, Michael introduced the ideas of the immunogenicity of synthetic antigens to the world of immunology.

Michael's favorite scientific discovery was not the successful invention of a therapy to treat MS. Instead, it was a basic science collaboration in the early 1960s with John Humphreys and Hugh McDevitt, who were then at the National Institute for Medical Research in Mill Hill, England (3). They became interested in the synthetic polymers that Michael had synthesized at the Weizmann Institute in Israel.* I was lucky to have both Michael Sela and Hugh McDevitt as my mentors in immunological chemistry.

According to McDevitt, there was some controversy about whether or not the synthetic antigens that Humphries and he tested were immunogenic at all. The Mill Hill scientists started with one of Michael's synthetic peptides (T,G)-A-L, where a poly-lysine backbone had side chains of tyrosine and glutamate. As McDevitt tells it, his boss, John Humphries (4), "wrote to Michael Sela saying that (T,G)-A-L appeared to be a poor antigen. Michael replied, with some heat, that it was a perfectly good antigen in his rabbits at the Weizmann Institute for Science in Rehovot, Israel."

Humphries listened to Michael's forceful response, then went back and immunized different strains of rabbits with the (T,G)-A-L polymer that Michael had synthesized. Only then, did he see that in some genetic strains of rabbits there were strong responses, while in other genetic strains there was almost no response at all.

McDevitt and Michael then clarified these promising results with a classic experiment in highly inbred mice with a set of synthetic peptides all having the same backbone of poly-L-lysine, but with different short side chains, one with a tyrosine and glutamate sidechain (T-G)-A-L, another with a phenylalanine and glutamate side chain (Phe-G)-A-L, and a third with a histidine and glutamate side chain (H-G)-A-L.

The persistence of Michael, along with Humphries and McDevitt, in studying these synthetic polymers opened the field of the genetic control of the immune response. In their classic paper (4), certain inbred strains were high responders to some of the peptides and low responders to others. McDevitt wrote that while some strains were strong responders to (T,G)-A-L, and nonresponders to (H,G)-A-L, other strains of mice "revealed exactly the opposite pattern … and the ability to respond was inherited as a dominant trait" (5).

The discoveries in the field of the genetic control of the immune response may have been the first remarkable example of how persistence provided dividends in Michael's scientific career. However, the most dramatic example of persistence in science came in discovering the first approved vaccine-like therapeutic for the disease MS. The process took place over a quarter of a century. Working together with Michael's first graduate student, Ruth Arnon, Michael,

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*Hugh McDevitt passed away on April 28, 2022, in Stanford, California.

Ruth, and a young researcher, Dvora Teitelbaum showed in a 1971 publication (6) that the synthetic approach to peptide polymers could be useful in studying autoimmune disease. This time, instead of ordered copolymers, they synthesized a random copolymer of tyrosine, glutamate, alanine, and lysine, rather than the ordered polymers with the same amino acids, used to study the genetic control of the immune response.

Michael, Arnon, and Teitelbaum had intended to show that this random copolymer containing the same molar concentrations of the four amino acids—tyrosine, glutamate, alanine, and lysine, found in the major protein of myelin—could induce paralysis in an animal model of MS. This would obviate trips to the slaughterhouse to obtain bovine spinal cords. The experiment did not succeed as planned. The random copolymer did not cause paralysis in experimental animals.

So instead, Michael's team decided to see if the random copolymer could prevent paralysis when the experimental animals were injected with a highly encephalitogenic myelin protein. When the initial plan to induce paralysis failed, they went to the backup plan, trying to see if the inverse of the original idea would work. The random copolymer, known as Copolymer-1, protected experimental animals from paralysis in the model of MS. Michael, Arnon, and Teitelbaum first published on this successful vaccine-like copolymer against MS in an animal model in 1971 (6).

Going from the laboratory bench to the patient's bedside is a slow trek. In 1987 Michael, Arnon, and Teitelbaum published a seminal paper in the *New England Journal of Medicine* (7) showing that the copolymer, named Copaxone, could block relapses in MS. Nine years later in 1996, Copaxone was approved by the Food and Drug Administration (FDA). From the initial publication on Copolymer-1 to its approval by the FDA took a quarter of a century, epitomizing persistence! Copaxone has been one of the most widely used therapeutics in MS and has been used by more than a million individuals with MS (Fig. 1).

Sela had other notable successes with inventions in cancer therapeutics, leading to Erbitux and other approved cancer drugs. Michael used some of his royalties from Copaxone and Erbitux to support a fund in the Office of Technology Transfer, named Yeda, at the Weizmann Institute. The dividend of persistence enabled a financial dividend, called the Yeda-Sela Fund. This fund supports basic research that might not be initially attractive to conventional funding agencies (2). Michael's persistence and understanding of the long and winding road to the implementation of fundamental discoveries likely drove his desire to fund unconventional ideas.

Fig. 1. Left to right: Murray Bornstein, Ruth Arnon, Michael Sela. Image credit: Ruth Arnon (photographer).

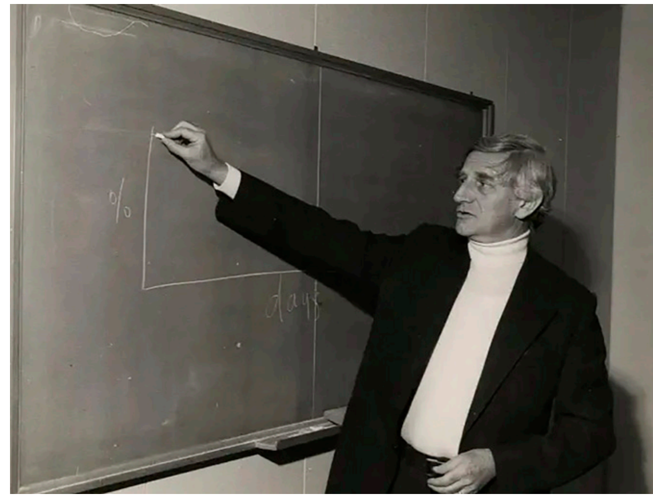

Fig. 2. Michael Sela at work. Image credit: Weizmann Institute of Science.

Michael was comfortable in the laboratory setting as well as in the administration of scientific research. As Chair of the Immunology Program at the Weizmann Institute, he created a department named Chemical Immunology. While he was president of the Institute for 10 years, he might on the same day have lunch with a Prime Minister and then attend a research laboratory meeting with young scientists. The Chemical Immunology Department had Friday morning seminars, and Michael regularly sat in the first row. He asked remarkably insightful questions. He was loyal and supportive of the younger members of the department (Fig. 2).

Among the young scientists in his department under his guidance was Zelig Eshhar, inventor of the chimeric T cell, which has revolutionized cancer therapy. Eshhar was elected as a Foreign Member of the National Academy of Sciences in 2022. In an interview that Eshhar gave to the Israeli paper *Ha'Aretz*, he mentioned how Michael guided him to the appropriate mentor for his postdoc: "For my post-doctorate [in 1973–1976], I wanted to go to a laboratory in New York, but Sela told me, 'You're a young person with three children. New York is no place to raise children. Go to Boston. I have a friend there who will take you in.' On the spot, Sela made a phone call, and so I arrived at Harvard, at the laboratory of Prof. Baruj Benacerraf, who later—in 1980—was awarded the Nobel Prize [in Physiology or Medicine] for his research about T cells. It was under Benacerraf, a Jew whose parents were of Moroccan and Algerian origin, and who had immigrated to the United States, that I became interested in cancer" (8).

While President of the Weizmann Institute, Michael invited Michael Levitt to return from his fellowship with Francis Crick to establish a Department of Chemical Physics. Writing his Nobel Prize biography, Levitt stated that "Michael

Sela, then president of the Institute, supported me tremendously. In 1980 he appointed me chair of the Department of Chemical Physics and at about the same time helped me get elected to EMBO [European Molecular Biology Organization] so that I could serve on the Scientific Advisory Committee of the European Molecular Biology Laboratory (EMBL) in Heidelberg. The Weizmann Institute also bought me a Vax 11/780 computer, a color frame buffer display, and a high-speed Vector General black and white display. With these wonderful conditions, I produced a series of nine sole-author papers in three years" (9).

Michael's career emphasized a brilliant synthetic approach to chemistry. But his persistence enabled him to guide major discoveries and to build and develop new therapeutics. Even while doing groundbreaking science, Michael was an inspiring teacher and advisor to many generations of students. His role in the development of young scientists touched many who later changed the world with their own discoveries.

Michael was a leader of science on a global scale. As noted, he served as President of the Weizmann Institute for a decade, from 1975 to 1985. He also served as President of the International Union of Immunological Societies. He played distinguished advisory roles as Chair of the Council of the European Molecular Biology Organization and served on the Global Advisory Committee of the World Health Organization. Michael was a member of the Israel Academy of Sciences and the Humanities, he was a foreign member of the US National Academy of Sciences, the Pontifical Academy of Sciences, the Russian Academy of Sciences, and the French Academy of Sciences.

With his wife, Sara, Michael was a strong supporter of the arts in Israel, including the Batsheva Dance Company and the Israel Philharmonic Orchestra. Michael is survived by Sara and three daughters (2). Over the years, we celebrated many of the numerous prizes and honors that were bestowed upon him. However, the generations he mentored with care and encouragement, not to mention his remarkable ideas, remain his best and most enduring prize. And thus, the succeeding generations of scientists provide a wondrous and continuing legacy.

Michael was the rare scientist who made an imprint not only through his discoveries with synthetic chemistry, but via his many roles as a statesman of science, making wise and lasting decisions along the way. Michael Sela was a sage.

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