Biochemical and Biophysical Research Communications 464 (2015) 376–378

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Historical review

Historical perspective: An interview with renowned Immunologist Dr. Michael Sela

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ARTICLE INFO

Article history:
Available online 20 May 2015

Introduction

Dr. Michael Sela is best known as the pioneer of synthetic antigens, which led to several important discoveries in vaccine design based on synthetic molecules that can trigger the immune system and drugs to combat autoimmune disease such as myasthenia gravis and multiple sclerosis. His multiple sclerosis drug ***Copaxone*** has become one of the most ground breaking discoveries in the field and helped many patients with this deadly disease. Dr. Carafoli recently interviewed him to gain more insight into his scientific path and discoveries in the field of genetic control of immunity.

Normally, I begin by asking how and when one got interested in science. It is a good way to start. However, in your case, questions on your early life must be asked first. You were born in Poland and left for Romania at the age of 11. Why did your family decide to leave Poland and then 6 years later, to move to Palestine? Was it because they had foreseen what would happen to Jews in Poland and then, later on, because life was slowly becoming unbearable in Romania as well?

My birth name was Mieczyslaw Salomonowicz and I was born in a Polish town called Tomaszow Mazowiecki. My grandfather started a textile factory which became very successful and exported material all over Europe. By the end of World War I, the factory was totally wiped out except for its long term debt for wool from Australia. My father, the youngest of seven siblings, started from scratch, rebuilt the factory, paid off the debt and again became successful. His clients in Romania urged him to come to Romania and build or run a factory there. As the Polish government became more and more anti-Semitic and working in Poland became harder and harder, my father accepted an invitation from a group of Jewish merchants in Romania and moved there in 1935. My father became the director of the biggest textile factory in the city of Craiova. The chairman of that company was the former Minister of Finance in Romania. When the first pogroms and murder of Jews started in Romania, he came to my father and told him that he was a close friend of the British Ambassador in Romania and that he could arrange visas for my father's family to anywhere in the British Empire. My father correctly assessed the situation in Romania and chose to immigrate to Palestine. After getting the visas, we went by boat to Istanbul, by train to Aleppo in Syria, from there to Lebanon and finally, we arrived in Haifa. We were very fortunate to escape the Nazi atrocities in Europe.

Palestine in 1941 must have been a place of great excitement for a 17 year old boy. One would have expected a period of adjustment, yet you immediately enrolled in the School of Chemistry at the Hebrew University in Jerusalem. So now comes my "standard" question: Why did you choose chemistry? Had the science "bug" already infected you, and if so, when had that happened?

I was born in the courtyard of a family-owned textile factory that made high quality worsted wool yarns and fabrics. Therefore, from a young age, I always thought I would go either into what was called at the time "synthetic chemistry" or into industry. In addition, I had a communist-leaning uncle who was an inorganic chemist at the Kaiser Wilhelm Institute in Berlin. He was offered a 10-year contract to create a scientific institute in Moscow, which he accepted on condition that he would get a one month vacation every year in the French Riviera. On his way to the Riviera he would always stop by our house in Poland. I liked my uncle very much and, maybe subconsciously, this too led me to choose a career in science.

When I arrived in Tel Aviv at the end of February 1941, I worked for several months as a weaver in a factory that made gauze for the British war effort. In the autumn of 1941, I started studying chemistry at the Mount Scopus campus of the Hebrew University. Even though studying took most of my time, I spent my free time reading literature, especially comparative literature. I was fortunate to be close to the National Library in Jerusalem where I was able to freely enjoy many fine works of literature.

After graduating in chemistry and a period which I suppose was probably a postgraduate study at the University of Geneva, you left science for a few years, becoming involved in activities

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http://dx.doi.org/10.1016/j.bbrc.2015.05.039

which were humanitarian or political. What prompted you to move in that direction and what brought you back at the age of 26 to the folds of science at the Weizmann Institute, which was to remain your lifelong scientific house?

I actually finished my M.Sc. in biochemistry at Hebrew University and was planning to do a PhD at the University of Geneva under the guidance of Prof. Kurt Meyer, a prominent polymer scientist of German Jewish descent who had escaped to Switzerland from Nazi Germany. I was on the verge of starting my doctoral studies when the UN vote for partitioning Palestine to a separate Jewish and Arab state was passed in 1948. I then met a recent graduate from Meyer's lab, Edmond (Eddie) Fischer (who later won the 1992 Nobel Prize in Medicine). Eddie helped me in my first days at the university and later we became very close friends when we were both in the United States. After several months in the university, I left Geneva to help in the struggle for Israel's independence and ended up in Prague. When the State of Israel was officially declared, I worked for two years as a commercial secretary in an Israeli legation in Europe. The Jews left in Europe after WWII were almost all holocaust survivors and my main function was to bring as many Jews out of war-torn Europe to Israel as I could. During this period, I held on to my goal of continuing in science and in August 1950, I started pursuing my PhD studies under Ephraim Katzir Katchalski at the newly opened Weizmann Institute of Science in Rehovot Israel and have stayed there ever since.

Your approach to the Weizmann Institute was through the door of biophysics, but in a short time you started working on immunology. I assume that a lot more than immunology was open to you when you first entered the Weizmann Institute. Is there anything that you would like to tell us as to why you were attracted to immunology?

There were two Katzir Katchalski brothers in the Weizmann Institute, Ephraim and Aaron. Aaron was the head of the Polymer Department, and Ephraim was the head of Biophysics. Aaron was working mainly on poly-electrolytes, and Ephraim was working on poly-amino acids and I was more interested in poly-amino acids. Ephraim was my mentor and he later became President of the State of Israel. After his term of presidency concluded he returned to the world of science at the Weizmann Institute. We remained close friends throughout till his passing away in 2009.

It was obvious to everybody that poly-amino acids have physical and chemical properties. I was interested in whether they have biological properties as well. We started with a protein, gelatin, which was known to be non-immunogenic. We attached poly-tyrosyl chains to gelatin, and this poly-tyrosyl gelatin became very immunogenic. A 3% poly-tyrosyl gelatin produced antibodies to gelatin, whereas a 10% poly-tyrosyl gelatin produced antibodies to tyrosyl peptides. Ruth Arnon, who was at the time my first PhD student, was paramount in the development of the different gelatin-based polypeptides. I was interested in understanding what was causing the immuno specificity. At that time, I decided to use a poly-lysine backbone and connect poly-tyrosine groups to the poly-lysine. We called this a multi-chain polymer. This multi-chain polymer was the first totally synthetic antigen. Much of the work on this synthetic antigen was done by another early PhD student of mine, Sarah Fuchs. This totally synthetic antigen allowed researchers around the world to study the molecular basis of antigenicity. Questions such as the minimum size of an antigenic molecule, the need of a charge on an antigen molecule, whether both polymers of L and D amino acids are immunogenic and other basic immunology questions could now be answered.

These synthetic antigens led to another great discovery. Together with John Humphrey, we discovered the genetic control of the immune response. I gave John a synthetic antigen which he injected into Holland Lop rabbits. However, he was not able to produce any antisera. I was puzzled, as our rabbits produced antisera after being injected with the same synthetic antigen. John then tried injecting the multi-chain polymer into another breed of rabbits (Dutch rabbits), and these rabbits produced the same amount of antisera as the rabbits that we had. When the antigen was injected into New Zealand White rabbits, John got double the amount of antisera. Together with Hugh McDevitt, we then experimented on mice and found that when tyrosines were switched to histidines, the antisera results in the different mouse breeds were reversed. We serendipitously discovered that certain poly-amino acid chains were immunogenic on certain strains but completely non-immunogenic on others. In parallel to Baruj Benacerraf, we independently discovered the genetic control of the immune response. As I said before, I initially was looking for biological effects of my synthesized multi-chain polymers. The immunological effects seen with the different synthetic antigens piqued my interest in immunology and I have stayed interested in this field ever since.

You are of course a stellar figure in immunology and your contributions to the area, beginning with those on synthetic antigens and on the genetic control of the immune response, have been monumental. The number of awards and honors that your work has generated is absolutely staggering and I would have problems making choices. Thus, let me be bold and ask you the following, which is the finding in the area of Immunology which you consider as the most important?

Although Copaxone, the drug for multiple sclerosis, which has greatly improved the quality of life of so many people, is my most important practical discovery, I think my most important discovery is the genetic control of the immune response. This discovery has led to the development of whole new fields in immunology. I received the Interbrew-Baillet Latour Health Prize of Belgium mainly for this discovery. Since then, I have also made important discoveries in the field of cancer. Lately, I have been working on pancreatic cancer, which till today has a 5-year survival rate in the single digits. We have developed specific antibodies for certain pancreatic cancer receptors. One exciting discovery was that giving two antibodies simultaneously for a certain receptor is more effective than one antibody and giving one of these antibodies together with chemotherapy has a synergistic effect. I would also like to mention that for the last 20 years I have been working with Yossi Yarden on using aptamers for cancer therapy. Similar to my first studies on polymers, we found that a triplicate of certain 14-mer sequence has a much better effect than a single, double or quadruple chain. I am now 90 years old and even if I will not see it in my lifetime, I think that aptamers will become very efficient disease fighting molecules.

I have mentioned the brief engagement in enterprises outside the direct area of science in your earlier career, but one aspect that characterized your entire career, beginning maybe in the early 1960's has been your continuous involvement in activities of general science policy at the Weizmann Institute in Israel, at national and international levels. Your role in making the Weizmann Institute one of the leading research institutions worldwide is largely acknowledged, but you have also been one of the founders of EMBO. I still remember the meeting we had in Heidelberg in which we initiated the EMBL in 1975. You had come surrounded by a group of body guards (terrorism was a very real threat in those days) and you had certainly impressed all of us. What is your appreciation of the significance of the launching of EMBO and the EMBL?

EMBO was created by the energies of Max Perutz and John Kendrew. Researchers at the Weizmann Institute have enjoyed a long and fruitful relationship with EMBO. One interesting fact that

portrays this close relationship is that of the 100 founding members, ten were from Israel: nine from the Weizmann Institute and one from the Hebrew University. I was one of the founding members and the fourth chairman of EMBO, responsible for choosing Heidelberg as the location for the EMBL labs and starting the EMBO Journal. EMBO and EMBL have always been and continue to be fantastic successes. With science becoming increasingly complex and thus increasingly expensive, the shared resources and collaboration at EMBO and EMBL enable the advancement of science for the benefit of the European community and the world.

Perhaps the most widely acclaimed discovery you have made is the wonder drug for one of the most important autoimmune diseases, multiple sclerosis. The story of Copaxone has been told a number of times, but could you please tell us again, in a few words, how you came to the idea of it?

We discovered early on that a Pro-Gly-Pro polymer cross-reacts with collagen. We were also able to take a small piece of lysozyme, crosslink it to a peptide and get antibodies against lysozyme. I had read in an article that when myelin basic protein is damaged, it causes multiple sclerosis. I thought that if we took a slightly positively charged synthetic polymer and inject it into an animal, the animal would get multiple sclerosis symptoms and then we would have an animal model on which to study the disease. We prepared four polymers and called them co-polymer 1, 2, 3 and 4 or in short, cop-1, 2, 3 and 4. We tried to induce the disease using these co-polymers for over a year without success. It later turned out, to our complete surprise, that instead of inducing the disease, the peptides were curing it. When the time came to name the drug, we decided to use the name of the polymers, cop, and add to that the suffix "axon", which sounded neuronal (multiple sclerosis being a neuronal autoimmune disease). Thus Copaxone was born. Although the initial idea was mine, I must also give major credit to Ruth Arnon, who pushed this project forward and to our PhD student Dvora Teitelbaum.

We have mentioned your activities in areas which are not directly related to bench-type science but are still in the broad sense related to science. However, there is an important aspect of your personality which is not related to science at all, and that is your involvement in the world of arts, especially music. I believe one could call it a hobby, but from what you told me on other occasions this is something more than that. You have befriended very prominent artists, let me only mentioned Arthur Rubinstein, and have sponsored and still sponsor artistic enterprises and institutions. How important has your keen interest in arts been to your life as a scientist? Has it helped you in your scientific development?

Science is about truth and art is about beauty and emotion. Both science and art satisfy my curiosity and I love them both. Art in all its forms enriches mankind regardless of occupation. Even when I had little money or time, during various scientific meetings, I always tried to attend the provided cultural activities. I later had the honor of befriending Arthur Rubinstein late in his life and I was the one to convince him to have the Arthur Rubinstein piano competition in Israel. The famous violinist Pinchas Zukerman told me once that his first recital at the age of 9 was at my house. I very much enjoy music festivals around the world and have donated money towards such events and towards other forms of art such as the Batsheva Dance Company here in Israel. I also love Jazz and through the years I met many famous jazz musicians such as Dizzy Gillespie and Thelonious Monk. My wife is also a great lover of the arts and was the director general of the Israeli Philharmonic Foundation for nine years. I cannot judge whether my artistic interests have enhanced my scientific acumen but they have definitely afforded me great pleasure. It will be for other to decide on this question.

The last question, especially with a person in your position and age category, is mandatory. You have witnessed very important advancements and changes in science and have certainly developed a global vision of its present perspectives and problems. If a young student were to approach you for advice, would you tell him to take science as a lifetime activity? And if yes, which problems would you outline for him/her as the most important?

I have only mentioned a few of my direct and indirect PhD students. I actually have a sort of "family tree" which includes over 400 people who were either my direct PhD students or students of those students etc. This accomplishment makes me very proud and also allows me a certain unique perspective. There is nothing greater than being a successful scientist and nothing more painful than being a mediocre one. Therefore, the first thing that a young scientist needs is the passion to do science. Optimism and perseverance are other qualities that successful scientists must possess. Thankfully, we are blessed at the Weizmann Institute with many such scientists.

Regarding the most important scientific endeavor, I do not know, and I will be foolish to try to prophesize where the next great discoveries will be. While neurology and nanotechnology are very popular and fashionable, the next breakthrough in science may come from a bright scientist in a small lab in any country in almost any field. Such a discovery can open new vistas and have a huge impact on us all. Therefore, my advice to bright young scientists is to pursue their chosen field with great passion, and with a bit of luck, great discoveries will follow.