A HEALTHCARE REVOLUTION IN THE MAKING

The Story of César Milstein and Monoclonal Antibodies

Collated and written by Dr Lara Marks

Today six out of ten of the best selling drugs in the world are monoclonal antibody therapeutics. One of these, Humira®, which is a treatment for rheumatoid arthritis and other autoimmune conditions, was listed as the top selling drug across the globe in 2012 with a revenue of US$9.3 billion. Based on its current performance many predict the annual sales of the drug will surpass the peak sales of Lipitor, a treatment for lowering cholesterol, that is the best selling therapeutic of all time. Currently monoclonal antibody drugs make up a third of all new medicines introduced worldwide.

Portrait of César Milstein.
Photo credit: Godfrey Argent Studio

Monoclonal antibodies are not only successful drugs, but are powerful tools for a wide range of medical applications. On the research front they are essential probes for determining the pathological pathway and cause of diseases like cancer and autoimmune and neurological disorders. They are also used for typing blood and tissue, a process that is vital to blood transfusion and organ transplants. In addition, monoclonal antibodies are critical components in diagnostics, having increased the speed and accuracy of tests. Today the antibodies are used for the detection of multiple conditions, ranging from pregnancy and heart attacks, to pandemic flu, AIDS and diseases like anthrax and smallpox released by biological weapons. Beyond human healthcare, monoclonal antibodies help detect viruses in animal livestock or plants, prevent food poisoning and investigations into environmental pollution.

Monoclonal antibodies are indispensable in so many walks of daily life thanks to their ability to target a single type of cell. Produced in the laboratory, these antibodies are derived from naturally occurring proteins made by the body's immune system to recognise and fight foreign invaders, such as bacteria and viruses. The antibodies are generated through the fusion of a myeloma cancer cell with spleen cells taken from an immunised animal.

Yet the story of how these unsung microscopic heroes came into the world and helped change healthcare remains largely untold. Moreover, their significance was largely overlooked at the time of their creation. The journey of monoclonal antibodies all started when an Argentinian émigré called César Milstein arrived at the Laboratory of Molecular Biology in Cambridge, the same laboratory where Francis Crick and James Watson discovered the structure of DNA in 1953. It was to be here that Milstein, together with Georges Köhler, pioneered the seminal technique for the production of monoclonal antibodies in 1975 and showed their clinical application for the first time.

This exhibition of the life and work of César Milstein provides a window into the world where monoclonal antibodies were first developed. Showing Milstein's notebooks and writings for the first time, this exhibition provides first-hand the complexities that were involved in the creation of monoclonal antibodies and brings to life the many challenges scientists face in devising a viable biotechnological tool and its application in healthcare. Transforming monoclonal antibodies, which started life as a laboratory tool into something that could be of use in the outside world was neither straightforward nor inevitable.

From Milstein's papers we learn first-hand how the newly-created monoclonal antibodies spread from the confines of Milstein's laboratory in Cambridge to scientists across the world and were then adapted for clinical applications. They highlight the logistical difficulties Milstein and his team faced in transporting monoclonal antibodies to other laboratories, and the fact that other scientists initially had little idea about how to grow and maintain the antibodies, let alone any idea what purpose they might serve.

Strikingly, initially Milstein had very few requests for monoclonal antibodies. By 1977, however, he was being inundated with requests for samples and had to search for outside support in the distribution process. This was to pave the way to the earliest commercialisation of the technology with the help of Sera-Lab, a small British company set up to supply animal serum reagents to the scientific community. The relationship between Milstein and Sera-Lab illustrates the process of technology transfer in biotechnology during its formative years. All of this was done with little public fanfare and no venture capital or government support. Yet, the collaboration between Milstein and Sera-Lab laid the foundation for the wide-scale commercialisation of monoclonal antibodies.

The exhibition also offers a way of understanding why the original technology developed by Milstein and Köhler was not patented in Britain and instead formed the basis of patents taken out by the Polish-American virologist, Hilary Koprowski, and his team based at the Wistar Institute in Philadelphia. The latter were thus the first scientists to be granted patents for monoclonal antibodies. Generating major controversy in the late 1970s, the patent story told in this exhibition reveals some of messy business of patenting research science and the implications this holds for those working in both the laboratory and the commercial world.

It also provides some insight into Milstein's very early efforts to demonstrate the practical application of monoclonal antibodies. He and his colleagues paved the way for the use of monoclonal antibodies as tools for the purification of natural compounds for drugs and as reagents for blood typing. Their work also demonstrated the use of monoclonal antibodies as probes to investigate the pathological pathway of neurological conditions and a wide range of other diseases. This paved the way to the adoption of monoclonal antibodies as diagnostic tools and an invaluable platform in the move towards personalised medicine. The final part of the exhibition shows how Milstein encouraged the use of genetic engineering to improve the safety and efficacy of monoclonal antibodies thereby enabling their use as therapeutics on a large scale.

Milstein's early life and work >>

Sponsored by the Medical Research Council as part of its Centenary Programme.

Supported by the Department of Social Science, Health & Medicine, King's College, London

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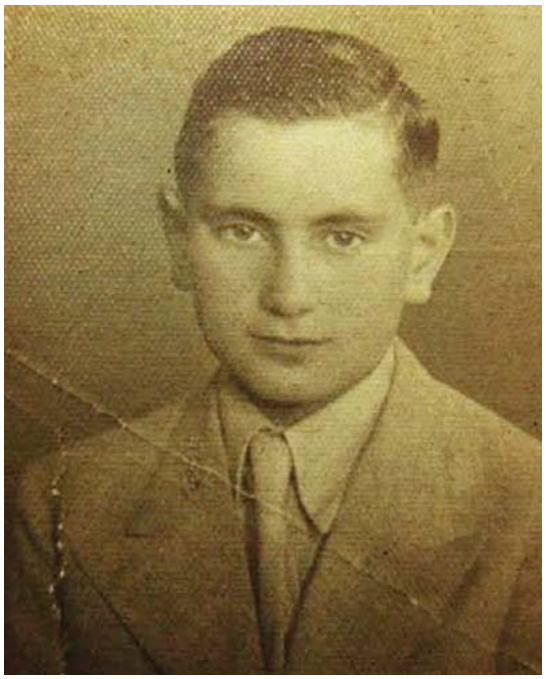
Milstein's early life

The journey from Argentina

The son of Jewish immigrants, César Milstein grew up in Bahía Blanca, a port town located by the Atlantic ocean some 500 miles south of Buenos Aires. Jews had begun to settle in Bahía Blanca from around 1900, many of them coming from central and eastern Europe.

Family background

Milstein's father, Lazaro, was born in a village in the Ukraine and migrated to Argentina in 1913 at the age of 14 with his aged aunt and uncle. For many years he lived in Jewish settlements near Bahía Blanca trying his hand at different trades, including farm labour, carpentry and railway work. During this time he taught himself Spanish and was an enthusiastic reader. He was also active in social and cultural activities, helping to preserve Yiddish literature and working for non-religious Jewish organisations, some with anarcho-syndicalist connections.



This photograph was taken when Milstein was a young man.

Photograph credit: Celia Milstein.

Lazaro met Maxima, his wife-to be, in Bahía Blanca. Maxima was born in Argentina. She was the daughter of poor Ukrainian immigrants who made great sacrifices to ensure she had a secondary school education and went to college. At the time Lazaro met Maxima she was a school teacher. Soon after their meeting, Maxima rose to become a head mistress. From 1926 to 1933, Maxima directed School No.3, the first co-educational school established in Bahía Blanca. Milstein, the middle of three brothers, was born at the family home on this school's premises. He also attended the school in his early childhood. Both of Milstein's parents spoke Yiddish at home, but Milstein was raised speaking only Spanish.

During his early childhood Milstein preferred playing with other children in the streets to reading books. With his mother's encouragement, however, he soon began to find pleasure in books, particularly adventure stories such as Rudyard Kipling's *Jungle Book*. Milstein developed a desire to pursue science at the early age of 8. This was prompted by a discussion he had with one of his cousins who had just completed her degree in Chemistry and was then working as a biochemist at the Instituto Malbran. Milstein was particularly fascinated by his cousin's description of her attempts to extract snake venom to treat snake bite victims. Milstein's interest in science deepened when on his ninth birthday he was given a Spanish translation of Paul de Kruif's *Microbe Hunters* by his mother. This book awakened his desire to have the same type of adventurous life like that of the scientists Antoni van Leeuwenhoek and Louis Pasteur described in the book.

Milstein grew up in a family which prized knowledge and education. Until his last year of school, Milstein attended schools close to home in Bahía Blanca, including the Colegio Nacional. In his final year, however, he moved to a secondary school in Buenos Aires to prepare for the entrance exam of the University of Buenos Aires.

Milstein's parents always supported his research, his mother helping to type up his first PhD thesis and his father offering him economic assistance so that he could dedicate himself to his doctoral research. Fiercely independent, Milstein declined his father's financial support.

Education

In 1945 Milstein started to study chemistry at the University of Buenos Aires. His undergraduate studies, however, were interrupted when,

Google Map showing the location of Bahia Blanca in Argentina. The town is a major trans-shipping and commercial centre, known for its large export trade of grains, wool, oil and fruit. Click to view a larger map.

during a faculty picnic, he suffered severe injuries to his pancreas when he hit a log while diving into a shallow pool and had to take off some time off to recover. He finally received his BSc in chemistry in 1952.

During his undergraduate years Milstein was active in campaigns against the Peronist government's policies aimed at privatising education and their more general impositions on universities and student life and rose to be President of the Student Union. At the time the government was clamping down on any political activity, and the atmosphere was particularly tense. In 1951, for example, a chemistry student, Ernesto Mario Bravo, was arrested and tortured for 20 days as a result of protesting against the government. His arrest sparked a major student strike. More than 150 strikers were arrested and university administrators expelled the more prominent leaders of the student movement. In the end, however, Bravo was released. The student movement considered this a major achievement.

Three years later student unrest erupted once again when the Peronist regime imposed even greater control over the media, education system, trade unions and the legislative and the judiciary. In October 1954 students joined workers striking against the then deep economic and social crisis and increasing unemployment.

Shortly after Milstein returned to the University of Buenos Aires from his several months of convalescence, Milstein met Celia Prilleltensky, a fellow chemistry undergraduate. Their first encounter was at the laboratory bench, where they found themselves working alongside each other. Celia not only shared Milstein's scientific interests, but was similarly an ardent student campaigner for free education. A year after their graduation in 1952, Milstein and Celia married.

At the same time as getting married, Milstein began to look for a suitable doctoral supervisor. Initially he sought to work with Professor Luis Leloir, a distinguished Argentinian enzymologist. To this end he visited Leloir's workplace, an old house in Buenos Aires. On arrival he met what seemed to him an unassuming man carrying a basket. This turned out to be Leloir. Having no space to take Milstein on, Leloir instead referred him to the Argentinian biochemist Professor Andrés Stoppani.

Milstein recalled that Stoppani was 'one of the few and perhaps the only full-time Professor of the Faculty of Medicine in the University of Buenos Aires, perhaps the most important universities in Latin America, a full time professor who probably had a salary of about the same order of magnitude as a janitor, trying to do serious and honest research in a laboratory with no funds at all'.

Stoppani advised Milstein to take some time off before he started his doctorate in view of the tense political climate which was hostile to students such as Milstein who had actively campaigned against the Peronist government's policies in education. His advice encouraged Milstein to take a year long honeymoon with Celia exploring Europe.

By 1954 the political environment had begun to improve and Milstein began researching enzymes for a doctorate in biochemistry although he had no funding as there was none for students in this period. He was forced to support his studies by working half-days in the Laboratorios Liebeschutz, a clinical biochemistry laboratory. In later years Milstein argued that this part-time job had taught him the value of organising his time.

This photograph shows Milstein early on in his courtship with Celia Prilleltensky.

Photograph credit: Celia Milstein.

During his doctoral research Milstein had access to only the most basic equipment. Some idea of how poor the facilities were at the time can be seen from his recollections that Stoppani had 'to pay, from his own meagre salary, for the pound of yeast … needed from time to time in order to prepare … [the enzyme] aldehyde dehydrogenase.' He recalled, 'We survived on what was inherited from the golden days … from the Medical School and with reagents justified by teaching requirements'. The most precious piece of equipment in the department was a Warburg apparatus, which Stoppani did not allow anyone but himself to use.

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