Aron Moscona

1929-2009

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Anthony P. Mahowald

NATIONAL ACADEMY OF SCIENCES

ARON ARTHUR **MOSCONA**

July 4, 1921–January 14, 2009

Elected to the NAS, 1977

By Anthony P. Mahowald

Aron Moscona died on January 14, 2009, at the age of 87. He will be remembered as one of the most influential developmental biologists of the 20th century. Moscona was a true pioneer in our understanding of how undifferentiated cells within a developing embryo associate and communicate with each other to form the various types of tissues of the body. He discovered that tissue from warm-blooded animal embryos treated with the enzyme trypsin can be dissociated into single cells, but that the cells can then re-organize into tissue-like architecture. Furthermore, cells of the same type will cluster together even if they are taken from different species of animal. The trypsin-mediated dissociation of tissues technique developed by Aron is now a standard method to prepare cell suspensions, and is widely used in biological and medical laboratories. Aron's research set the stage for the discovery of most known cell-cell recognition molecules.

Early life and career

Aron Arthur Moscona was born July 4, 1921, in Haifa, Israel. He graduated from the Reali High School in Haifa, and then attended Hebrew University in Jerusalem, where he earned his Ph. D. in endocrinology-biochemistry in 1950. He spent two years as a post-doctoral fellow at the Strangeways Research Laboratory in Cambridge, England, before joining the faculty at the University of Jerusalem as an associate professor of Physiology in 1953. Aron later spent two years as an investigator at Rockefeller University in New York City, collaborating with Paul Weiss.

University of Chicago

He joined the faculty at the University of Chicago as an associate professor of zoology in 1958 and rose quickly through the ranks, becoming a professor in 1960. In 1974 he was named the Louis Block Professor of Biology.

Throughout his career, he enjoyed close collaboration with his wife Malka, a brilliant scientist who also rose through the faculty ranks and became a much-loved teacher of undergraduate developmental biology at Chicago. The couple ran the Moscona laboratory together for several decades.

At the University of Chicago, Aron was also instrumental in founding the Committee on Developmental Biology, a Ph. D. granting program that brought together faculty from both the basic science and clinical departments in common research interests.

Cell-cell recognition

Vertebrate tissues are composed of multiple types of cells, which assemble in specific patterns to perform their various functions. As a post-doctoral fellow at Cambridge, Moscona directed his attention to questions related to the emerging field of developmental biology, especially how different cell types arose from a fertilized egg cell and organized themselves into tissues and organs. He developed novel techniques to answer some of these questions.

As Masatoshi Takeichi, a leader in the cadherin field of cell biology, explains:

> *Animal tissues comprise multiple types of cells, which assemble in a tissue-specific pattern. Following the discovery by Rous and Jones in 19161 that trypsin, a proteolytic enzyme, can liberate cells from a mass of tissue cultured in a plasma clot, Aron Moscona found that this method is also useful for dispersing cells from freshly isolated chicken embryonic tissues, and furthermore discovered that these trypsin-dissociated cells can reaggregate and restore the original tissue-like architecture when cultured under proper conditions. Although similar phenomena had been previously observed in invertebrates and amphibian cells by other investigators, Moscona's finding was the first to demonstrate that the cells released from warm-blooded animals can re-establish a tissue-like association in vitro. Nowadays, the trypsin-mediated dissociation of tissues is a standard method to prepare cell suspensions, and is widely used in biological and medical laboratories.*
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> *In 1952, Aron published two monumental papers[2] reporting that limb rudiments and mesonephros of chicken embryos can be dissociated into single cells by treating them with trypsin, and that the dissociated cells can reaggregate when cultured in concave glass slides. Most importantly,*

Moscona proposed that vertebrate cells are equipped with a mechanism to recognize and associate with same cell types, and that this mechanism is conserved across species.

within the formed aggregates, identical cell types cluster together and different cell types segregate from one another, assuming the original tissue-like structure.

For example, the limb bud is comprised of cartilage, muscle, and skin, while the mesonephros comprises epithelial tubules and connective tissues. Each time the cells re-aggregated, all of these tissue components re-assembled in a pattern similar to that seen in the original tissues. Moscona subsequently found that, when cells collected from different animal species were mixed — for instance, mouse and chicken cells — cells derived from identical tissues were intermingled irrespective of the difference in species, whereas cells from different tissues were segregated, similar to results seen in experiments using a single species.

Based on these observations, Moscona proposed that vertebrate cells are equipped with a mechanism to recognize and associate with same cell types, and that this mechanism is conserved across species.

These discoveries, as well as some made by others during the 1950s and 1960s, stirred up controversy over the mechanisms underlying cell-cell adhesion and recognition. One major point in the dispute was whether the mechanisms controlling cell adhesion and sorting could be explained simply with physicochemical terms alone, or was dependent on the actions of specific biochemical molecules. Moscona clearly preferred the latter model, and hypothesized the presence of cell-type specific, intercellular adhesion molecules that are localized along the cell surface.

There were many observations made in his laboratory supporting this hypothesis: for example, he found that there are retina-specific cell surface antigens and that, when tissue cells are cultured in vitro, they release materials into the culture medium which enhance their own aggregation.

He also accumulated evidence showing that the putative adhesion molecules are trypsin-sensitive proteins and that these must be re-synthesized to allow the cells to re-aggregate once they are dissociated with this enzyme.

Cell and developmental biologists of the next generation built on the foundation of the ideas and experiments of Moscona, and were later able to identify trypsin-sensitive cell-cell adhesion receptors, one of which was termed cadherin. Cadherins are Ca^{2+}-dependent intercellular adhesion molecules, which can be digested with trypsin when Ca^{2+} is absent. Intriguingly, cadherins consist of multiple subtypes, which are expressed by different cell types. Each cadherin subtype has a binding specificity; that is, it preferentially binds to the same subtype. This homophilic binding nature of cadherins clearly explains the mechanism of how identical cell types cluster together. Thus, Moscona's hypothesis was substantiated, although the molecular properties of the real cell-cell adhesion molecules are a little different from what he expected; for example, the intact cadherin molecules are not released into culture medium, because they are transmembrane proteins.

One of Moscona's important advances was in the use of immunological tools to gain a molecular handle on cell-specific adhesion molecules. Dr. Paul Linser of the University of Florida, who was a post-doctoral associate in Aron's lab at this time, recalls, one of Aron's most insightful contributions to the field was the incorporation of immunological tools for the dissection of interacting molecules. Aron was one of the first to show that

antisera generated by immunizing an animal such as a rabbit with a crude membrane preparation had dramatic impact on the capacity of embryonic cells to self-assemble into tissues. By combining his earlier technical approach of dissociating embryonic tissues with proteolytic enzymes (such as trypsin), and then giving the single cell suspensions the circumstances that could foster cell-cell contact and sorting with antibody probes of cell surface molecules, he set the stage for the discovery of most of the now well known cell-cell recognition molecules (such as cell adhesion molecules, or CAMs).

Cell-cell interaction in the nervous system

In the 1960's Moscona switched his interest to the nervous system, in which the extraordinary complexity and cellular heterogeneity provided multiple examples for complex tissue organization and ultimately cell-specific gene expression. During the development of the eye and neural retina, arguably the most accessible part of the central nervous system, the Moscona laboratory discovered a specific marker of differentiation, the enzyme glutamine synthetase, whose activity rose several hundredfold during the first day of retinal development.

Aron further found that the sudden rise was actually a hormonally induced gene expression brought on by two events: the maturation of competency to respond to the hormone hydrocortisone, and the maturation of the adrenal cortex and the consequent elevation of systemic levels of cortisone. Subsequent work showed that the maturation of competency to respond to cortisone was in itself a cell-cell interaction-dependent phenomenon. That is, if the embryonic cells were dissociated into single cells, no such hormone response could be elicited. If those same cells were reassociated into tissue-like aggregates, competency for hormone stimulation emerged on schedule.

The eventual developmental paradigm that emerged was that the neuroglial cells of the retina, the so-called Muller cells, were the actual cells producing glutamine synthetase and that their maturation into a hormone-responsive state was driven by contact mediated interactions with earlier differentiating retinal neurons. This became a useful paradigm for the Moscona laboratory in further studies.

Aron was an important innovator in the cell-cell interaction field. His protocols and technical developments were the stimulus that led to a rapid growth in understanding of cell-cell association during the 1950's and 1960's. As Masatoshi Takeichi recalls,

I was fortunate to have the opportunity to hear from Aron himself about his discovery of trypsin-mediated cell dispersion. In a meeting, he used a microscope to display trypsin-dissociated cells. Someone took a look and said, 'They are dead!' As a young scientist, Aron was terribly discouraged by such a statement. But this is a typical example of how true pioneering discoveries are not always immediately accepted by the scientific community.

Urs Rutishauser, one of the discoverers of the neural cell adhesion molecule (NCAM) in Gerald Edelman's laboratory, recalls Aron's strong influence on the field as shown by his frequent publication and enthusiastic presentation of his results. Moscona was the major stimulus for others as the field grew, Rutishauser says.

"Aron's efforts were extraordinarily imaginative, wide ranging in scope and truly of seminal significance in the field of developmental biology," said Donald Steiner, A. N. Pritzker Professor of Biochemistry and Molecular Biology.

"He did fundamental work that was way ahead of his time, with significance extending basic biology into areas such as cancer metastasis," said colleague Ralph Weichselbaum, the Ludwig Professor and Chairman of Radiation and Cellular Oncology. "He was also a decent guy…he extended a lot of guidance and support to me when I first came to the university."

Elaine Fuchs, one of Aron's colleagues at the University of Chicago, is an active researcher in epithelial tissue biology. She remembers him fondly, saying

When I first met Aron in 1980, he was already one of my scientific heroes. We had many memorable scientific discussions, which had a major impact on my own career in skin biology and development.

Aron also had enormous patience with me. This is perhaps best exemplified by the wonderful collegiality and generosity he showed me as a new Assistant Professor when one day, during a failed experiment in the laboratory on the floor above Aron's office, I flooded his desk and soaked a grant proposal beyond repair. Others would have lectured or shouted at me. Aron simply called me to his office, and began talking about science when I realized what had happened. He and Malka never wavered in their support of me and they served as a true inspiration throughout my life.

Linda Degenstein, who joined the Moscona lab as an undergraduate student and stayed for 13 years until Aron retired, recalled that

> *Aron had a deep love of science and could spend hours on the microscope looking at immunohistological slides and taking pictures. This was a new technique in the lab and fairly new in its development. He wanted to see every aspect and make sure that he had the whole picture before he could commit to a theory.*
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> *In addition to science, Aron had a love of music and the arts. I remember once several members of the lab were planning on going to a Peter, Paul and Mary folk music concert at Ravina. Malka said to me "you should tell my husband that you are going." I looked at her and said we were going on a Saturday evening so it wouldn't affect time in the lab. She convinced me to go see Aron and tell him. In a very deep voice, I remember him saying "Linda, I hear you are going to a Peter, Paul and Mary concert. Do you know I am a big fan of theirs?" It turned out that Aron wanted us to ask him and Malka to go to the concert. We all had a great time.*
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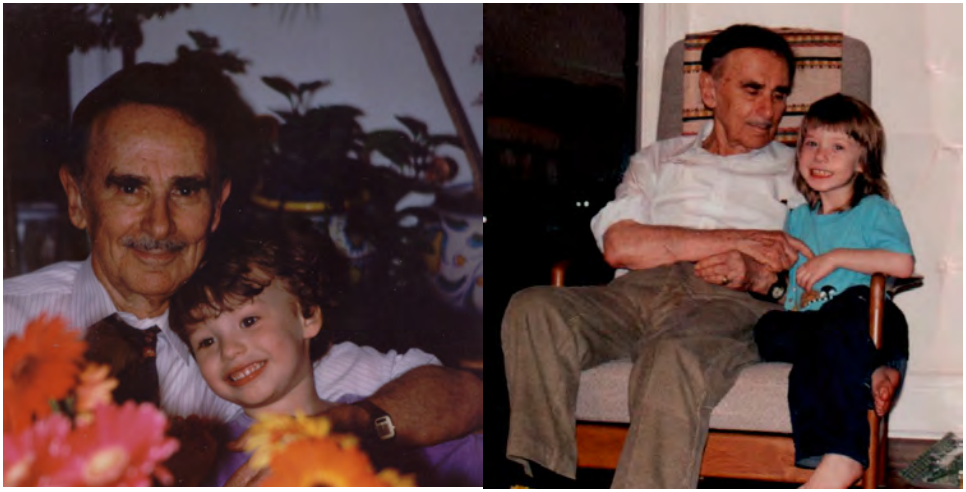
> *The Mosconas were like family to me. On one occasion on a visit to their home, Aron showed me his collection of slingshots, and he was very proud to have built box frames for them. Aron and Malka would spend vacations in areas where tourists don't usually venture just so that they could see the folk arts produced instead of the commercially available ones for tourists.*

Publications and honors

Aron was a prolific author, publishing 261 scientific papers, many of them co-authored with Malka. He was co-author of an introductory textbook, *Concepts in Developmental Biology*, and served as founder and co-editor of the annual publication *Current Topics in Developmental Biology*. As his co-editor David McClay of Duke University recalls, when Aron was editor of *Current Topics in Developmental Biology*:

> *Leaders in each area of developmental biology were solicited and the book was widely respected for its coverage. Alberto Monroy, Aron's great Italian friend and co-editor, would arrive for a week or two to choose authors. That friendship with Monroy, who was the director of the Stazione Zoologica in Naples (now called Stazione Zoologica Anton*



Moscona with grandson Jacob (left) and grandson Ari (right).

Dohrn), and perhaps Aron's closest friend in science, was a happy time each year for him. They argued, laughed, and earnestly discussed each topic and author before arriving in agreement with the annual list of invited authors.

Aron was active in the International Society of Developmental Biology, and served as its president from 1976 to 1980. He was a member of several national advisory panels including the President's Biomedical Research Panel in 1975. He was the chair of the board of scientific counselors of the National Institute of Child Health and Human Development from 1982 to 1986. He served on an NIH advisory panel on human fetal tissue transplantation in 1988, and lent his passion to demonstrating the importance of continuing this work. For much of his career he served on grant review boards for the March of Dimes, where he found the company of like- minded scientists and clinicians dedicated to the advancement of science for the benefit of humanity. He was a member of the board of governors of Tel Aviv University from 1984 until his final illness.

He was a member of the National Academy of Sciences and American Academy of Arts and Sciences, including its Italian counterpart, the *Accademia di Science e Lettere*. He received many awards, including the Claude Bernard Medal in Experimental Medicine

from the European Association for the Study of Diabetes, Japan's Azabu Gold Medal and the Alcon Prize in Visual Sciences.

Retirement

In 1991 Aron became Emeritus Professor of Molecular Genetics & Cell Biology and of Pathology. He retired in 1992 and moved with his wife, Malka, to New York to be near their daughter Anne, a professor at the Weill Medical College of Cornell University in New York City, and her sons Jacob and Ari. He lived there until his death on January 14, 2009, at the age of 87. "As a grandfather," Anne recalls, "he was very nurturing, and both boys grew up with his loving example and his sense of humor." He took his two grandsons to their classes, picked them up from school, and took them to the playground, cooked dinners for them, "bought them books," she added, "and instilled a love of learning and debate, history, music, art, and, of course, science. Both of them in their own ways hope to follow in his tradition."

NOTES

1. Rous, P., and Jones, F. S. 1916. A method for obtaining suspensions of living cells from the fixed tissues, and for the plating out of individual cells. *J. Exp. Med.* 23:549-55.
2. Cell suspensions from organ rudiments of chick embryos. *Experimental Cell Research* 3:535-539, and The dissociation and aggregation of cells from organ rudiments of the early chick embryo. *J. Anat*. 86:287-301.

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