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Obituary

Avraham Ben-Nun—Pioneer, fighter, friend

Avi Ben-Nun, Professor of Immunology at the Weizmann Institute of Science, died of lung cancer on January 18, 2019. We, his friends and colleagues for some 40 years, write these words in memory of a unique scientist and teacher of life (Fig. 1).

Throughout his scientific career, Avi Ben-Nun was fascinated by immune tolerance and its pathological version, autoimmunity. How do T cells discriminate the body's own tissues and tolerate them, and, conversely, how can these cells be misled to attack self-structures, creating autoimmune diseases?

The time when Avi stepped into the world of autoimmune research was during the late 1970s, a time that could be best described as the dawn of cellular immunology. Back then, most immunologists adhered to early, strict versions of Burnet's Clonal Selection Theory. They believed that immune tolerance relies on the physical elimination of autoreactive immune cells from the immune repertoire; contrariwise, autoimmunity would be driven by "forbidden clones" arising following pathological mutation. Young Avi Ben-Nun was not convinced by this theory and by its experimental foundations. He looked for ways to question the theory experimentally.

An opportunity to examine the problem directly opened, when he joined the Cohen lab. This was the time when the groups of Irun R. Cohen and Hartmut Wekerle (HW) had decided to join forces; the goal was to isolate and expand putative autoimmune effector T cells isolated from rats actively immunized with myelin antigens to induce experimental autoimmune encephalomyelitis (EAE). Indeed, the HW lab had developed an approach to physically isolate autoimmune T cells, but, unfortunately, the model used was autoimmune orchitis, a model without a known autoantigen. On the other hand, Irun R. Cohen was experienced in EAE, a paradigm sharing features with human multiple sclerosis (MS), and involving a defined brain autoantigen, myelin basic protein (MBP). The ongoing question that puzzled us was if it would be possible to isolate and clone MBP specific effector T cells and use them as probes to decipher autoimmunity in the brain?

Avi gladly accepted this challenge. After studies of EAE in Israel, he moved to the lab of HW in Germany and started to purify MBP-specific T cells from rats with EAE. These cells were exquisitely specific for the autoantigen, MBP, but, regrettably, the available methods did not allow keeping them alive in culture. He returned to Israel and worked on culture conditions that kept the selected T cells alive, allowing the establishment of T cell lines and clones. Then came the memorable day, when a cable from Rehovot arrived to Germany: "EUREKA: THEY (the recipient rats) BECAME SICK!!!": Avi had succeeded in producing an MBP-specific T cell line, which could be propagated in culture seemingly without limitation, and, most importantly, when injected into healthy syngeneic rats, produced classical paralytic EAE.

This was a true breakthrough, which, incidentally, was not easy to sell. One of the leading journals flatly rejected the report, arguing that the paper merely described "available techniques applied to EAE"—uninspiring. The *European*

Figure 1. Fellowship: Hartmut Wekerle, Avi Ben-Nun, and Irun R. Cohen, from left to right.

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Journal of Immunology was more perspicacious, and there, this paper became one of its most-cited articles [1].

Avi Ben-Nun used autoimmune T cell lines and transfer EAE for a spectrum of questions. He determined the interaction between autoantigenic peptide sequences with MHC class II determinants. Importantly, paralleling Claude Bernard, he identified the MOG peptide 35–55 as the dominant encephalitogen in C57BL mice, mice which had been considered to be resistant to EAE induction [2]. Because C57BL mice are the standard strain used for therapy, transgenesis, and other manipulations, MOG EAE is now used by numerous laboratories throughout the world. In further studies, Avi investigated the brain structures that might provide encephalitogenic autoantigens were such autoantigens present only in myelin, or could neuronal or glial structures serve as well? He identified β-synuclein as a neuronal encephalitogen. Furthermore, Avi also studied microbial effects on EAE, and explored regulatory pathways and therapeutic applications [3].

Avi Ben-Nun's work has fundamentally influenced the field of autoimmune research, both conceptually and methodologically. To name a few examples, cloned autoimmune T cell lines allowed direct studies of the T-cell receptor repertoires used in autoimmune responses. Engineered T-cell clones have been used as reporters to trace the complex interactions between migrating effector T cells and the body; importantly, these T cells have helped shed light on immune reactivity within the CNS, and have led to the localization of autoimmune activation in other sites such as in the intestinal milieu. Finally, T-cell-mediated autoimmune models have given rise to the development and validation of therapies of human autoimmune diseases.

Most important, however, Avi's work has revolutionized our concepts of immunological tolerance. Isolation of pathogenic T-cell populations from genetically unaltered organisms (human as well as rodent) formally demonstrated the presence of potentially autoreactive T-cell clones in the healthy immune system. It established that these clones remained dormant in the healthy body, but can be transformed to pathogenic effectors by misguided activation processes.

Avi's contributions to immunology have been inspiring, but his life story is inspiring in its own way. Avi was born in 1947 in a small village in Yemen isolated from any academic or scientific environments. When Avi was 2 years old, his family, along with other members of the ancient Jewish Yemenite community, was airlifted to Israel in the wake of the Arab-Israel war. Avi and his family were absorbed into a transit camp where their home was a tent; to support the family, Avi's father found work as a farm laborer in a local settlement. It was difficult to support the growing family, and Avi was sent to a boarding school. There his natural curiosity flourished, and he discovered an interest in living creatures and an attraction to biology. After finishing high school, he was inducted into the army, where he was wounded by a bullet in the abdomen that penetrated his spine, rendering him paralyzed from the waist down. His physicians concluded that he would never be able to walk; his future was perceived as mobility by wheelchair. But Avi's fighting spirit and determination prevailed and, after an intense year of hospitalization and physiotherapy, he acquired the ability to walk again, albeit with a significant limp. Avi returned to his studies, and his research achievements led him to an independent laboratory and to the rank of Full Professor at the Weizmann Institute.

Avi overcame poverty, early academic isolation, immigration into a new culture, and severe physical injury to make a significant mark on science and, ultimately, on human wellbeing. His life is an inspiration, no less than his science. We mourn his passing, as we rejoice in his spirit.

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