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Legends of Allergy/Immunology: Polly Matzinger

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Polly Matzinger's work has mainly been focused on two fundamental questions in immunology and therefore also relevant to allergy. First, how does the immune system know whether to react or not against a given molecule.[1,2] Second, if it reacts, how does it determine the type of immune response it will choose (e.g. IgG_1, IgG_4, IgE, IgA, Th1, 2, 3; CTL, etc).[3] Polly is both a theoretician who challenges existing dogma to shape future discoveries and an experimentalist who succeeded in deepening our understanding of how the immune system "works".

The daughter of a WWII Dutch resistance fighter and holocaust survivor and a French ex-nun, Polly Celine Eveline Matzinger migrated to the USA with her family in 1954, when she was seven years old, under a French quota, though the family was living in Holland at the time. After living in several places (i.e. New York, California, Colorado) Polly graduated from the University of California, Irvine. In her late twenties, while working as a bartender in Davis, California, her intellect was noticed by a local professor who persuaded her to take up science. In 1976 she joined the laboratory of Dick Dutton at the University of California in San Diego to do a PhD in Immunology. At this time, San Diego also had a collection of other immunological royalty, including Mel Cohn, Mike Bevan, Susan Swain, John Kappler, Pippa Marrack, and Rolf Zinkernagel, among others. Polly's thesis work provided the model of alloreactivity that we still quote today,[4] and with Mike Bevan she described cross priming. Three years later Polly joined the laboratory of Herman Waldmann at the University of Cambridge, England, where she demonstrated, for the first time, that T-cell tolerance was MHC-restricted. In 1983, she joined the Basel Institute of Immunology (BII), Basel, Switzerland. In this creative and collaborative environment, where each member was assigned a small budget and a technician, she authored six publications in six years, three of them in Nature. It was at the BII that she first coined the term "professional" antigen presenting cell to describe APCs (i.e. DCs and macrophages) that can activate naïve CD4 T cells, and showed that B cells are semi-professionals, since they can activate memory but not naïve T cells.[5] With all of these accomplishments early in her career, Polly was already a legend in immunology.

In 1989, she was recruited as a "special investigator" by Ronald Schwartz at the Laboratory of Cellular and Molecular Immunology (LCMI) (Figure 1B), at the National Institutes of

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CONFLICTS OF INTEREST

The author declares that she has no conflicts of interest other than being Polly Matzinger's former Staff Scientist at NIH

Health, Bethesda, Maryland, USA. For the following 24 years Polly headed the Section of Immunological Tolerance and Memory, best known as the Ghost Lab, a name given to the lab during the nine months it remained unoccupied while Polly immersed herself in chaos theory, exploring its capacity to predict the immune response. At the Ghost Lab she continued her work on the role of B cells as APCs, further showing that they can induce either tolerance or activation of CD4 T cells, depending on whether the CD4 T cells were naïve or previously activated, respectively.[6] Her most revolutionary work, developed in discussions with Ephraim Fuchs, is the set of essays postulating the Danger Model of Immunology where, in dramatic contrast to the established dogma, she proposed that *damage,* and not the *non-self* nature of an antigen, is what triggers an immune response[1,2] (Figure 2). Her model brought a new perspective able to explain numerous immune phenomena. Regarding allergy, McFadden and Basketter appreciated that the "recently proposed danger model may be an illuminating alternative for studying allergic contact dermatitis". Polly proposed that toxic chemicals and allergenic proteases might initiate allergy by the direct damage of dendritic or other cells, and she further expanded by defining three categories of allergens: those that themselves cause damage, those that are packaged with something that causes damage, and those that mimic endogenous alarm signals.

She populated the Ghost Lab with postdocs having broad interests and backgrounds, and such diversity was manifested by the different areas of research and models that were being studied at any particular time in the lab (oral tolerance, parasitic infection, DC activation, transplant tolerance, tumor rejection, newborn immunization, gut homeostasis, just to name a few). The postdocs were encouraged to follow their own paths, even if not directly testing the Danger Model, but always with the invaluable intellectual feedback from Polly. This medley of personalities and projects ensured that no lab meeting, or coffee break, ever contained a dull moment. As a result, Polly published outstandingly high-quality work in very diverse areas of immunology, usually challenging the current dogma in that particular field (Table 1).

While discussing science, Polly often says "God is in the details". Accordingly, when something doesn't make sense she will dig for those details until either a clearer explanation appears or the conversation causes everyone to reexamine their assumptions. During this intellectual process Polly focused her efforts to be clear and to the point, even if that was at the expense of wordy politeness. In this way she might have stepped on the toes of some larger-than-life personalities, but the objective was always to encourage discussion with the purpose of bringing light to relevant questions.

Polly's life outside the lab is as interesting as her research, and her creativity has been fostered while spending time with her border collies (i.e. observing her sheepdog led to one of the main tenants of the Danger Model). She is, indeed, an accomplished dog trainer who competed for the US team at the world herding finals, and she is bringing a new breed of sheep (Gotlands) into the USA.

Although the Ghost Lab was closed in 2013, Polly continues to be a valuable member of the NIH community and she is finishing, through collaborations, a study on why the measles vaccine doesn't work in young babies.

In an era of “omics” and sometimes too fast-paced science, we need more meticulous and brilliant thinkers like Polly to build logical scaffolds on which to place the almost infinite amount of information available. Indeed, much of Polly’s early work is a sobering lesson on how to face down large volumes of complex cellular data and conflicting interpretations to distil meaningful theories and come up with new and revealing experiments.

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Figure 1.

A, Polly in 2019 at the NIH library. Photo by Ainhoa Pérez-Díez. B, Polly (in black, front row) with members of the three labs that formed the Laboratory of Cellular and Molecular Immunology at NIH in 2000.

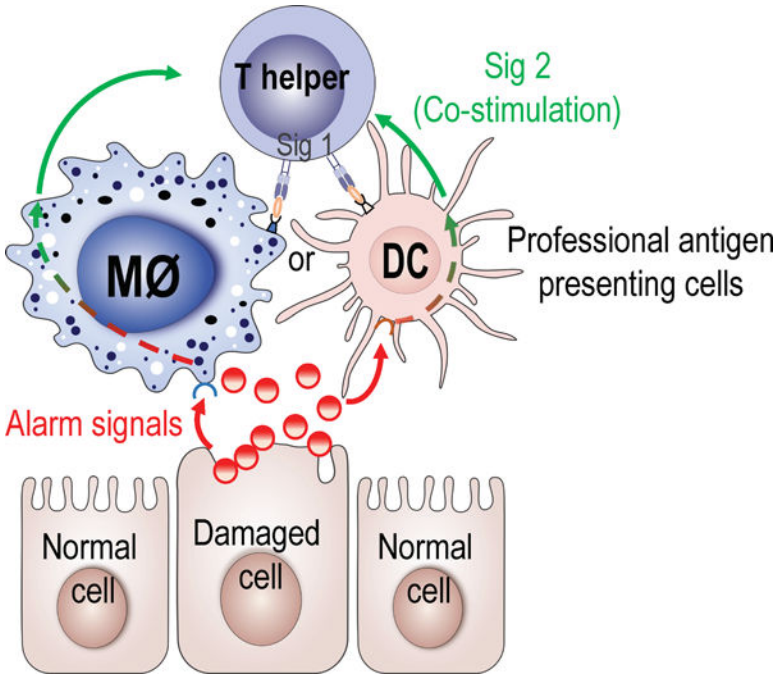

Figure 2.

Danger Model. Professional antigen presenting cells (Macrophages or DC) are activated to stimulate T cells by endogenous cellular alarm signals released from distressed or damaged cells.

Table 1.

Polly Matzinger's major contributions in chronologic order

1. A model for alloreactivity, before it was understood that MHC molecules bound peptides, essentially the model we still use today (1977).[4#]
2. Antigen presentation by B cells to naïve CD4 T cells does not induce activation (1988).[5#] but instead induces tolerance (1992).[6#]
3. The Danger Model of Immunology, suggesting that an immune response is not triggered by recognition of non-self but instead by recognition of damage (danger) (1994, 2001, and 2002).[1,2*]
4. Antigen exposure in newborns can be immunogenic, in contrast to contemporary belief that it would induce tolerance (1996).[7#]
5. The three-cell temporal bridge for cytotoxic CD8 T cell (CTL) generation, by which upon antigen recognition a CD4 T cell "licenses" a dendritic cell (DC) to become able to activate CD8 T cells into CTLs (1998).[8#]
6. The first evidence supporting the Danger Model: DCs can be activated by damaged cells in the absence of 'foreign' products (1999).[9#]

[#]These 6 articles combined have been cited more than 4,700 times

[*]These two essays account for more than 5,800 citations.