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This Week's Citation Classic®

McDevitt H O & Sela M. Genetic control of the antibody response. I. Demonstration of determinant-specific differences in response to synthetic polypeptide antigens in two strains of inbred mice. *J. Exp. Med.* **122**:517-31, 1965.
[National Institute for Medical Research, Mill Hill, London, England and Weizmann Institute of Science, Rehovot, Israel]

Immunization of CBA and C57 mice with the synthetic multichain polypeptide poly(Tyr,Glu)-poly (DL-Ala)—polyLys ((T,G)-A—L) in Freund's complete adjuvant resulted in a more than tenfold difference in the antigen-binding capacity of the sera. (The immune response was under definite genetic control, due to a single major genetic factor.) Immunization of CBA and C57 mice with (H,G)-A—L, in which histidine replaces tyrosine, gave the opposite result. Thus, the genetic control of the response to (T,G)-A—L and (H,G)-A—L is specific for the antigenic determinant. [The *SCI*® indicates that this paper has been cited in over 350 publications.]

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In the summer of 1961, I was returning to the Weizmann Institute in Israel from a year spent at the National Institutes of Health in Bethesda, Maryland, and I stopped in London to discuss with John Humphrey and Brigitte Askonas a collaborative effort to follow the fate of strongly radioactive synthetic polypeptide antigens and to find out whether antigen molecules must be present in antibody-provoking cells. Ultimately, this project was brought to a successful fruition,[1] but in its initial stages Hugh McDevitt, who joined Humphrey from Boston, injected cold poly(Tyr,Glu)-poly (DL-Ala)—polyLys ((T,G)-A—L) into rabbits to learn about their immune response.[2] Several weeks later, Humphrey informed me at a WHO meeting in Geneva that the sandylop rabbits they used did not produce antibodies, and we considered the genetic make up of the animal as one possibility to explain this result. Within a short time, it was clear that New Zealand rabbits produced as many antibodies as our rabbits in Rehovot, and Himalayan rabbits were almost an order of magnitude better.

At this moment, it was natural for McDevitt to switch to inbred strains of mice, and we showed for the first time, in the paper discussed here, the determinant-specific genetic control of immune response in mice. This is the main reason for the importance of the paper. In another paper, the study was extended to additional polypeptides, and the specificity of the genetically controlled immune response was further analyzed.[3] A short while later, McDevitt, making use of our multichain synthetic polypeptides, was able to show for the first time the link between immune response and the major histocompatibility locus of the species,[4] which in turn led to our present-day understanding of immune-response genes and their products. In our further studies on specificity, we have shown that the chemical determinants stimulating helper and suppressor responses are distinct and can be present simultaneously in the same molecule. Thus, addition of carboxy-terminal tyrosine residues to a (Glu,Ala) polypeptide converted this immunogenic molecule to an immunosuppressive molecule in mice bearing the H-2[s] haplotype.[5]

As is apparent from the above story, my contribution has been mainly chemical and immunochemical, whereas McDevitt contributed the major part of the genetic aspects of this study. McDevitt is today the chairman of the Department of Medical Microbiology in Stanford University Medical School, whereas I continue to be at the Department of Chemical Immunology at the Weizmann Institute of Science, where I returned recently full-time after a 10-year tour of duty as president of the Institute. The field of the genetic control of immune response has developed immensely since our initial observations.[6]

1. **McDevitt H O, Askonas B E, Humphrey J H, Schechter I & Sela M.** The localization of antigen in relation to specific antibody-producing cells. 1. Use of a synthetic polypeptide (T,G)-A—L labelled with iodine-125. *Immunology* **11**:337-51, 1966. (Cited 85 times.)
2. **Sela M, Fuchs S & Arnon R.** Studies on the chemical basis of the antigenicity of proteins. 5. Synthesis, characterization and immunogenicity of some multichain and linear polypeptides containing tyrosine. *Biochemical J.* **85**:223-35, 1962. (Cited 220 times.) [See also: **Sela M.** Citation Classic. *Current Contents/Life Sciences* **29**(37):19, 15 September 1986.]
3. **McDevitt H O & Sela M.** Genetic control of the antibody response. II. Further analysis of the specificity of determinant-specific control, and genetic analysis of the response to (H,G)-A—L in CBA and C57 mice. *J. Exp. Med.* **126**:969-78, 1967. (Cited 110 times.)
4. **McDevitt H O & Chinitz A.** Genetic control of the antibody response: relationship between immune response and histocompatibility type. *Science* **163**:1207-8, 1969. (Cited 295 times.)
5. **Schwartz M, Waltenbaugh C, Dorf M, Cesla R, Sela M & Benacerraf B.** Determinants of antigen molecules responsible for genetically controlled regulation of immune responses. *Proc. Nat. Acad. Sci. USA* **73**:2862-6. 1976.
6. **Schwartz R H.** Immune response genes of the murine major histocompatibility complex. *Adv. Immunol.* **38**:31-201, 1986.

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