

**Dankesrede**

**von**

**Prof. Dr. David G. Schatz**

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Anrede,

I am grateful and honored to receive the 2023 Paul Ehrlich and Ludwig Darmstaedter Prize. It is humbling to receive a prize in the name of Paul Ehrlich, whose revolutionary “side chain” theory of 1897 established the concept of the soluble antitoxin, or antibody—a molecule that Ehrlich presciently predicted could be secreted into the blood as a “receptor” to bind and neutralize toxins and microbes. I owe a particular debt to Ehrlich’s genius, because understanding the antibody is what first drew me to immunology.

My parents were both chemists and they created an intellectually fertile environment for my upbringing. I absorbed early on that research allowed one to discover things that no one else knew or had ever known. What an exciting idea!

I first encountered the intricacies of the antibody in graduate school. Not only can the immune system create a nearly limitless number of different antibodies, but it does so audaciously. The chromosomes we inherit from our parents cannot produce any antibodies at all. Instead, antibody genes must be assembled from far-flung bits and pieces of a chromosome in a “recombination” process that irreversibly alters the chromosome and typically deletes a substantial portion of it in the process. Back then, we did not know how such a recombination process occurred or what proteins were responsible. Big, exciting questions abounded. Could I, a new graduate student, help to answer them?

I had the good fortune to perform my graduate research in the laboratory of the brilliant David Baltimore at MIT, an exciting environment that encouraged ambitious goals and risk-taking. In my case, a lot of risk. Pursuing an approach that was widely expected to fail, I proved that the recombination process could be turned on by inserting genes into recombination-deficient cells. But which gene specifically was the key? It was a daunting search for a needle in a haystack. I was joined in this search by Margie Oettinger, also a graduate student in the Baltimore lab, and despite predictions that we would never succeed, together we found the gene—only to discover, quite unexpectedly, that it was two genes, which produce two proteins, which we named RAG1 and RAG2.

RAG1 and RAG2 work together as “molecular scissors” that precisely snip pieces of DNA out of a chromosome to initiate the recombination process. Without them, the immune system can produce no antibodies.

RAG1 and RAG2 continued to present the field of immunology with numerous surprises over the ensuing decades, none more remarkable than the story of their evolution. My laboratory, in

parallel with another group, discovered that RAG1 and RAG2 not only snip a piece of DNA out of a chromosome, but can also insert the excised DNA fragment into a different piece of DNA in a reaction known as transposition. Pursuing the implications of this discovery has led my research back in time to when multicellular organisms were first appearing on Earth. Current evidence indicates there then existed a “genetic parasite,” known as a transposon, containing the early ancestor of RAG1 and RAG2. This transposon survived by jumping from the genome of one organism to another. Eventually, one of its progeny found its way into the vertebrate lineage and triggered the evolution of our adaptive immune system, including our capacity to produce hundreds of millions of different antibodies. How wonderful that Paul Ehrlich’s antitoxins arise from the action of a tamed genetic parasite.

I am grateful to many people. David Baltimore and my award co-recipient, Fred Alt, are important role models, mentors, and supporters and my admiration for them is unbounded. Many other colleagues from my years in the Baltimore lab were, and continue to be, inspirations, advisors, and friends. My colleagues at Yale University, particularly in the Department of Immunobiology, have supported my career and exemplified excellence in leadership.

I extend heartfelt thanks to all the members of my Yale laboratory for dedication, insight, experimental skill, and exciting discoveries. Thomas Leu helped establish the cell expression systems that led to foundational breakthroughs, and Ferenc Livák patiently taught me the intricacies of lymphocyte development. Despite my insistence that there must be something wrong with their experiments, Alka Agrawal and Quinn Eastman revealed the mysterious “band X” and persevered to prove that it represented transposition by RAG1 and RAG2. Yuhang Zhang, with important help from Tat Cheng and Yong Xiong, elegantly combined structural biology and biochemistry to reveal fundamental aspects of RAG function and evolution. Chang Liu and Yang Yang redefined what I thought possible in their brilliant structural analysis of the earliest known ancestor of RAG1.

I am very grateful to my parents and brothers for unflagging love and support and to my extended Schatz family for their warmth and for encouraging an irreverence for convention. To my children, for love, creativity, guidance in the evolving language of our society, and showing how much improvement there can be from one generation to the next. And, finally, to my wife Susan, the anchor of my life, for patience, insight, love, and understanding.

Thank you, again, to the Scientific Council, Board of Trustees, and President of the Paul Ehrlich Foundation for this honor.