

**Public Lecture by Dr. Michael Karin**  
**“How We Defend Ourselves From Infections”**

**Wednesday, September 22, 2004 at 6:00 p.m. in the Garren Auditorium, Basic Science Building**  
**Sponsored by the Sam & Rose Stein Institute for Research on Aging, UCSD**

A. Introduction

I am originally from Tel Aviv, Israel, where I obtained my undergraduate education in Biology and Biochemistry. In 1975, I arrived in the U.S. to enroll as a graduate student at UCLA in the newly erected Molecular Biology Institute. I received my Ph.D. in molecular biology four years later, in 1979. Ever since my undergraduate days, I was interested in the use of a combination of genetic and biochemical approaches to unravel the basic secrets of life. I am particularly interested in learning how cells regulate the use of genetic information (the information stored in DNA or our genome) in response to signals provided either by hormones or by the environment in which they live. This is one of the most fundamental and central problems in molecular biology.

In trying to understand how cells regulate the use and deployment of genetic information, we began to study a special class of regulatory proteins called transcription factors. These are proteins that bind to regulatory sites on DNA and determine whether genes are switched on or off. We began to study one specialized transcription factor called nuclear factor kappa B (NF- $\kappa$ B). NF- $\kappa$ B acts as a switch. It is usually present in the cytoplasm of cells, outside of the nucleus – the compartment in which the genetic information (DNA) is stored. Under these conditions, NF- $\kappa$ B is inactive. However, in response to signals that are generated by invading viruses, bacteria and fungi, NF- $\kappa$ B is turned on (activated) and it enters the nucleus. Once in the nucleus, NF- $\kappa$ B turns on the expression of a large number of genes that are required for mounting a successful immune response. Such an immune response is required for fighting microbial and viral invaders.

B. Field of Study

By studying how NF- $\kappa$ B is activated and regulated, I became interested in studying the immune response to microbial and viral pathogens. We are particularly interested in studying the earliest type of immunity called innate immunity. Innate immunity provides us with the first line of defense to microbial and viral infections. It is an essential line of defense that is active within minutes of an infection. In addition to fast killing of invading microbes and viruses, innate immunity is required for activating the second line of defense called adaptive immunity. Adaptive immunity takes many days or weeks to be switched on, but because it entails the production of specific antibodies, it can provide us with long-lasting protection. Sometimes we can trigger adaptive immunity at will through a process called vaccination. But even successful vaccination requires the activation of innate immunity.

Innate immunity, therefore, is essential for life. Worldwide, more death and misery are caused by infectious diseases, the diseases caused by invading microbes and viruses, than any other disease. Even in the U.S., with our state-of-the-art healthcare system and wide availability of modern sanitation and antibiotics, infectious diseases result in a very large number of deaths and a huge loss of human productivity. In addition to causing death, or less serious but debilitating consequences, viral and microbial infections are thought to be a major risk factor in various cancers, accounting for at least 20% of cancer deaths worldwide. In addition, chronic or

overstimulation of the innate immune system can be a major factor in the etiology (development) of autoimmune and chronic inflammatory disorders, such as inflammatory bowel disease.

Current treatments and prophylactic measures for infectious diseases, none of which will be discussed in my talk, include good sanitation, clean water, safe food preparation and refrigeration, antiseptic procedures, vaccination, and the use of antibiotics.

Instead, I will focus on the basic fundamentals guiding the operation of the innate immune system, what we can learn from these principles regarding the development of new therapeutic strategies, and how dysfunction or chronic activation of the innate immune system can lead to the development of chronic inflammatory diseases and cancer.

### C. Research Endeavors

Our present research focuses on the functions of NF- $\kappa$ B in activating the innate immune system to microbes and viruses. In particular, we are studying the role of NF- $\kappa$ B in maintaining the viability of inflammatory and immune cells, the kind of cells that protect us from infections. By killing these cells, several very nasty bacteria can establish super-virulent and lethal infections. I will discuss research that suggests new strategies for limiting the death of such cells, thereby augmenting our innate immunity to such infections. We also study how chronic stimulation of NF- $\kappa$ B can lead to the development of chronic inflammatory bowel disease and cancer.