

Public Lecture by Dr. K. George Chandy, M.D. Ph.D.
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“A Novel Therapy for Autoimmune Disorders”
Wednesday, May 19, 2004 at 6:00 p.m. in the Garren Auditorium, Basic Science Building
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Autoimmune diseases such as multiple sclerosis, type-1 diabetes mellitus, and rheumatoid arthritis are a disease threat to several million people worldwide. In multiple sclerosis, immune cells called lymphocytes destroy the myelin sheath that covers nerves in the central nervous system, leading to paralysis, urinary incontinence, blindness, and death. Proteins in the myelin sheath are recognized via specific receptors (antennae) on the surfaces of immune cells, and as a result, these immune cells get activated. Repeated stimulation by myelin proteins causes these cells to change from a naïve, uninitiated state into aggressive effector memory cells that contribute to the immune-mediated damage to the nervous system. Strategies designed to specifically inhibit the function of these disease-causing effector memory cells without globally impairing the function of the immune system might therefore have value in the treatment of multiple sclerosis and other autoimmune diseases. We are developing a novel therapeutic approach for autoimmune disorders that involves the selective blockade of a potassium channel (called Kv1.3) in disease causing cells.

Kv1.3 is a protein on the surface of lymphocytes that is responsible for allowing potassium ions to leave or enter cells. This potassium channel controls the membrane potential (the small voltage difference between the outside and inside of the cell membrane) of lymphocytes and thereby regulates the entry of calcium into these cells. Calcium is necessary for the activation of cellular processes and the development of the immune response.

We recently found that myelin-recognizing effector memory lymphocytes from patients with multiple sclerosis exhibit elevated numbers of Kv1.3 channels. A specific Kv1.3 blocker called ShK that we isolated from the Caribbean Sea anemone *Stichodactyla helianthus*, shut down these disease-causing cells without impairing the function of naïve and early memory lymphocytes. This suggested the possibility of using ShK to target myelin-recognizing effector-memory cells that contribute to multiple sclerosis. In a proof-of-concept study, normal rats given myelin-recognizing effector memory lymphocytes developed a severe disease called experimental autoimmune encephalomyelitis that mimics multiple sclerosis, and ShK completely prevented and treated the disease. We have also developed a fluorescent version of ShK that may have use as a diagnostic test to detect the disease-causing effector memory cells in the blood of patients with multiple sclerosis. In conclusion, the Kv1.3 channel in lymphocytes may be both a therapeutic and a diagnostic target for multiple sclerosis and other autoimmune diseases.