

# A Nanoscale May Lead to New Asthma Treatments

By observing how certain immune cells gather information about foreign invaders, School of Medicine researchers may have found a novel type of therapy for asthma.

The therapy hinges on a mechanical movement measured in nanometers—one-billionth of a meter—in the bull’s-eye-shaped immune synapse. Discovered in 1995, the immune synapse is named after the synaptic junctions that transmit signals between brain cells because it similarly carries information between immune system cells.

The micromechanics in this bull’s-eye allow immune cells called T-cells to move from cell to cell. In their travels, T-cells interact with other cells through the immune synapse and detect protein flags that identify foreign invaders such as parasites or bacteria. T-cells assess these flags and, when necessary, they fight back.

The discovery of the mechanics underlying the immune synapse, described in the journal *Cell*, is a step toward demystifying how the structure works. Moreover, it points to the potential for a completely new type of therapy for asthma based upon nanoscale mechanical intervention, according to Michael L. Dustin, Ph.D., the Irene Diamond Professor of Immunology and Professor of Pathology, who led the study, supported by an NIH-funded Nanomedicine Development Center grant.

What would this nanomechanical intervention look like? “We don’t really know for sure,” says Dr. Dustin, “but maybe we can reinforce synapses with nanostruts.” He aims to stabilize the immune synapse because his observations suggest that this could impede the generation of T-helper 2 (Th2)-cells. Th2-cells are specialized T-cells that fight parasites, but they also produce compounds known to cause asthma.

Dr. Dustin first observed the mechanics

that drive a T-cell’s motion in time-lapsed movies. The movies show that when the bull’s-eye shape distorts to form a crescent, the cell moves. When the bull’s-eye reforms, the cell stops. These observations suggest that the bull’s-eye resembles a lamellipodium, a structure used by many other cell types for locomotion.

To visualize how such a structure propels a T-cell from place to place, imagine that the cell is a tractor with treads that are always pulling inward. If these treads are arranged in a circle around the perimeter of the tractor, forming a bull’s-eye, the tractor will stop moving and remain in one place. If the treads reposition so that they pile up and form a crescent on one side of the tractor, the tractor will start moving.

To understand the molecular interactions governing the movement of these “treads” in the immune synapse, Dr. Dustin focused on protein kinase C- $\theta$  (PKC- $\theta$ ), an enzyme found in T-cells that is known to be involved in the immune synapse. He found that when PKC- $\theta$  is present, it breaks the bull’s-eye shape and causes the cell to move. When it is absent or inhibited, the bull’s-eye remains intact and the cell stable.

Dr. Dustin speculates that more-stable, less-mobile T-cells make fewer Th2-cells—those cells known to contribute

to asthma. If this hypothesis bears out, his findings suggest that PKC- $\theta$  is a potential target for an asthma therapy.

Other studies support this idea. One recent study was led by Dr. Dustin’s colleague, Dan R Littman, M.D., Ph.D., the Helen L. and Martin S. Kimmel Professor of Molecular Immunology and Professor of Pathology and Microbiology. It

found that PKC- $\theta$ -deficient mice are protected from asthma. Another recent study showed that the stability of a T-cell’s interactions with other cells affects the way it differentiates. This suggests, says Dr. Dustin, that one possible way to control the balance of Th2-cells in the immune system is by restricting the cell’s mobility and promoting longer, stabler interactions.

“Though inhibiting PKC- $\theta$  may have other effects on T-cell activation, [a PKC- $\theta$ -inhibiting] molecule is a potential drug for stabilizing T-cell interactions,” he adds.

What Dr. Dustin has in mind, however, is not necessarily a therapy based on a typical molecular inhibitor. “We could target the immune synapse physically with a mechanical intervention of some kind, fabricated at nanoscales.” A tiny strut to buttress the immune synapse against PKC- $\theta$  activity might be more specific and therefore less disruptive to other signaling pathways involving PKC- $\theta$  because it targets a physical structure rather than a chemical one.

“We would like to create a new kind of therapy [for asthma],” says Dr. Dustin. “That’s our big goal: out-of-the-box therapies based on nanotechnology.” ●

