

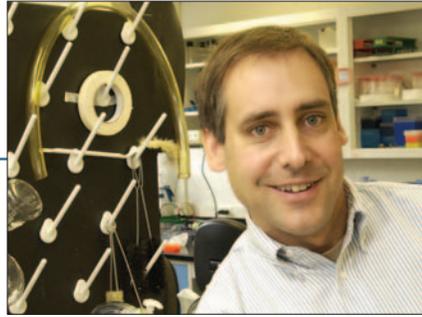
His eye's on microvilli

Lymphocytes are “guys in white hats” in more ways than one. They are circulating white blood cells and play a key role in battling villains like infections and inflammatory diseases. It's long been known that lymphocytes have numerous finger-like projections called microvilli. Over the past five years, it has become clear that microvilli serve a critical physiological function. Among those helping to advance understanding of the role of these “good guys” is Henry Higgs, Ph.D., an assistant professor of biochemistry at DMS.

Microvilli are believed to be important in guiding lymphocytes out of the rapidly moving blood stream into locations in the body where they are needed—a process called extravasation. The emerging picture is that tissue inflammation triggers the migration of molecular receptors from the interior membrane of the endothelial cells that line blood vessels to the cells' surface. When these receptors are exposed to slower-moving blood at the margin of a vessel, they appear to interact weakly with lymphocytes' microvilli.

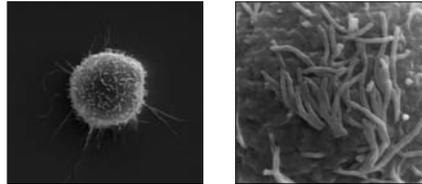
Receptors: Imagine a tumbleweed being blown up a narrow canyon, its outer stems catching on obstructions that gradually slow it down. Finally, it has been slowed enough to put down roots. Similarly, the tips of microvilli are almost certainly the initial contact with endothelial receptors that slow lymphocytes' momentum. But the anchoring mechanism is believed to be located at the base of microvilli. It seems likely, therefore, that there are two different kinds of docking apparatus involved in extravasation. The anchoring step causes the lymphocyte to flatten and elongate. Next, the lymphocyte worms its way between the tightly fitted endothelial cells, finally emerging on the tissue side of the blood vessel.

At that point, evidence suggests that the lymphocyte reassumes its normal



JON GILBERT FOX

Higgs, above, studies lymphocyte microvilli, below.



shape and proceeds to the site of the inflammation to do immunologic battle. Even in the absence of inflammation, lymphocytes routinely migrate to and patrol lymph nodes, apparently seeking out abnormalities that failed to elicit an alarm. It's not known what part, if any, microvilli play in other immunologic functions, such as antibody production, but Higgs is convinced they do have other roles.

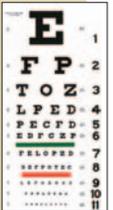
Many details remain to be worked out, but there is hope that extravasation can be exploited clinically. For example, the body's inclination to reject a tissue transplant is mediated largely by lymphocytes. Today, rejection is controlled with powerful but toxic immunosuppressant drugs that interfere with lymphocytes' function. If extravasation could be blocked or slowed, the body might more readily accept the foreign tissue—without the toxic effects of immunosuppressants.

There are other potential therapeutic applications. For example, if the migration of lymphocytes to arterial plaques containing cholesterol could be blocked, it might prevent the rupture of those deposits—a common cause of heart attacks and strokes. And many cancer cells share aspects of the extravasation process, accounting for their ability to metastasize, meaning the malignancy of some cancers could be reduced by destroying their microvilli. So the body's “white hats” may yet help investigators do battle with other bad guys. **ROGER P. SMITH, PH.D.**

Annual research funding to Dartmouth Medical School has increased by 58% since fiscal year 2001. For more on the most recent fiscal year's research income, see page 19 in this issue.

Visionary work

Zinc plays a critical role in the blinding disease retinitis pigmentosa, according to a group of researchers from DMS. The team determined that a zinc deficiency can cause malformation of a light-receptor protein called rhodopsin, which is essential for vision but is dysfunctional in those with the disease. The discovery reveals a possible “pharmacological



approach for the treatment of select retinitis pigmentosa mutations,” wrote the paper's authors. Their report was the “Paper of the Week” in the *Journal of Biological Chemistry*. Since the disease affects an estimated one million people worldwide, the public health implications of the work are promising.

Another look at Botox

In addition to treating wrinkles, severe underarm sweating, and certain neurological disorders, Botox may also be a safe and effective treatment for gastroparesis—a debilitating gastric disorder that causes nausea and vomiting and often affects diabetics. The finding came from a small study led by DHMC gastroenterologist Brian Lacy, M.D., Ph.D. The eight subjects were all type I diabetics. Before the treatment can be added to the list of Botox's approved uses, however, a double-blind, placebo-controlled trial is in order. ■

