JON GILBERT FOX

Wickner, on the far left, with some of the members of his lab, identified a key player in cell membrane fusion.

Investigators SNARE important cellular insight

Medical investigators are often quick to point out the likely practical applications of their discoveries—how they might be used to prevent or cure disease. But DMS biochemist William Wickner, M.D., is just as quick to explain that the practical value of his work is that it's laying a foundation for medical research.

Cell: His most recent finding, published as a feature article in the *Proceedings of the National Academy of Sciences* (*PNAS*), focuses on how certain proteins—called SNAREs, Rabs, and SM proteins—work in concert to promote cell membrane fusion. It's a process that is essential to cell growth, hormone secretion, and neurotransmission.

What has "allowed more rapid advance in the last 50 years in medicine than ever before has been the basic understanding of the constituents of our cells and how they're organized and how they function," says Wickner. "Understanding the normal basic biology has proven to be the essential framework for looking for what is wrong in various illnesses and disease processes."

But the path to understanding that biology can be long and arduous. For instance, research in cell membrane fusion has been ongoing for more than 20 years. In the 1980s and 1990s, scientists identified the lipids and proteins involved. At first, it was thought that SNARE proteins (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) were the core catalyst for the process. But soon Wickner and other researchers concluded that "in addition to SNAREs there were other proteins that were just as essential for the fusion event."

An earlier finding had thrown the field "into substantial confusion."

Still, "the lore in the field," says Randy Schekman, Ph.D., editor-in-chief of *PNAS*, "was that you could constitute fusion with SNAREs alone."

Fuse: Then, in 2006, researchers at two different institutions found that SNAREs alone could cause cell membranes to lyse, or break, as well as to fuse. This finding "threw the field into substantial confusion," says Wickner. Until then, the leading model was that the other proteins merely regulated the SNAREs but weren't absolutely necessary for fusion.

Wickner's previous studies, however, had suggested that other proteins were required for cell membrane fusion. So he continued patiently with his work. Using baker's yeast as a model, his lab sought to determine whether membrane fusion in a cell organelle called a vacuole is possible with SNARE proteins alone. Yeast serves as a good model for such studies because its components can be manipulated for *in vitro* (test tube) studies; then those results can be correlated with functions *in vivo* (in the whole cell or organism).

The investigators engineered yeast to overproduce four SNARE proteins, then controlled the levels of the other proteins and measured the properties of the fusing vacuoles. They confirmed that while vacuole membranes with high levels of SNAREs could fuse in the absence of other proteins, they often ruptured, too. It turns out that Rab and SM proteins are indeed needed to prevent the membranes from leaking or rupturing during fusion.

Hapless: The results show that "SNAREs by themselves are powerful but hapless," wrote University of Texas biochemist Thomas Südhof, M.D., in an accompanying commentary in *PNAS*. They "need to be organized by Rab and SM proteins."

Wickner is continuing his studies of cell membrane fusion in order to "understand it at a chemical level," he says. "This is a prerequisite to understanding membrane fusion throughout biology and even to beginning the process of screening for chemicals that can modify the process in pharmacologically useful ways."

Already, with the help of two postdoctoral fellows, he has succeeded in assembling pure proteins and putting them into a synthetic membrane that can fuse. This research is not yet published.

"I will be delighted if it turns out in the fullness of time that my work leads to an ability to intervene in a particular disease," Wickner says. "But to be honest, my strongest motivation is to understand the normal cellular biology." Laura Stephenson Carter