

The hunt for the cell's compass

September 2005 -- [Peter Devreotes](#) was looking for a research problem that would take him in a new direction. Finally, he found the compass he was looking for—literally and figuratively—in the amoeba, *Dictyostelium*.

In a decade of work, [Devreotes' team](#) has identified the molecules that allow amoebae to detect attractants and move purposefully toward them, edging forward on their pseudopodia or “false feet.” As a bonus, the efforts should shed light on how other cells move in response to external signals in wound healing, angiogenesis and embryogenesis, as well as in disease processes like asthma, multiple sclerosis, arthritis and cancer.

Devreotes' ground-breaking studies of chemotaxis began soon after he arrived at Hopkins as an assistant professor in the [Department of Biological Chemistry](#) in 1980. Then, he says, “the predominant view was that cells were kind of blind, that they felt their way around merely by adhesion.”

He felt intuitively that the perspective was wrong, but it took a long time to figure how to study a process that by its very nature required a whole functional cell. The traditional “break it apart to see how it's put together” strategy just wouldn't work for this particular problem.

“It was only about 10 years ago that we figured out a solution,” he says.

Even then, Devreotes adds, “the first successful thing we did was still pretty unsuccessful.” Using *Dictyostelium* as a model, he hypothesized that chemotaxis was initiated at the receptor level. Years earlier, he and his students had isolated a certain receptor—for cyclic AMP—and discovered that knocking out its encoding gene rendered the cells insensitive to chemoattractants. Replacing the missing receptors with new versions restored that ability—a great satisfaction.

But the researchers also assumed the receptors would move directionally, within the amoeba, toward the chemoattractant—cAMP—present outside the cell. The team was flummoxed when the receptors didn't rearrange themselves.

“They stayed uniformly distributed,” Devreotes says.

So they conducted a tunneling expedition of sorts, working back to discover the first protein in the pathway that either sensed the right direction or made the decision to head toward it. They ruled out activity at the G-protein level, although cells clearly use G-protein-linked signaling to detect chemoattractants.

Quite by accident, says Devreotes, the team stumbled on a protein with the requisite behavior. Not long after, they showed that it bound to a lipid called PIP3. Put into *Dictyostelium* and exposed to a chemoattractant, the PIP3-bound proteins moved dramatically to the front of the cells, “directing their movement,” he says, “like a needle on a compass.”

In the amoeba and later in human white blood cells, Devreotes and colleagues showed that under chemoattractant stimulation, PIP3 is generated at the front of the cell, taking only seconds to spark the pseudopodia that pull the cell along. Follow-up studies revealed that two enzymes, P13K and PTEN, regulate PIP3's production. The former moves to the front of the cell to synthesize the lipid while PTEN degrades it at the back of the cell.

“And those enzymes themselves move,” says Devreotes.

Still, he says, the team wasn't certain that PIP3 was the real controller. So [Miho Iijima](#), a postdoc in Devreotes' lab, spearheaded the next study, one to remove the PIP3-degrading enzyme and see what happened.

When Iijima created PTEN knockout cells and exposed them to a chemoattractant, pseudopodia took shape around the entire circumference of the cell. No longer at a leading edge, PIP3 had seeped around the whole perimeter. Without its “compass” the amoeba was pulled in multiple directions.

The fact that PTEN is a known tumor suppressor makes the team's finding particularly intriguing.

“PTEN is mutated in 50 percent of cancers,” Devreotes points out. “Damage or remove PTEN and you're on your way to a tumor.”

Likewise, too much PIP3 results in a glut of cell growth and greater cell motility, either of which could encourage metastases, he adds.

Now the group hopes to find what drives this process even earlier and whether it is relevant to all human cells or only a select few like white blood cells.

“We know many of the components of this signaling pathway and how many of the proteins are distributed. We still don't know what's determining the directional decision,” Devreotes says. “The focus now is how enzymes such as P13K and PTEN get to the right locations.”

– Deborah Rudacille