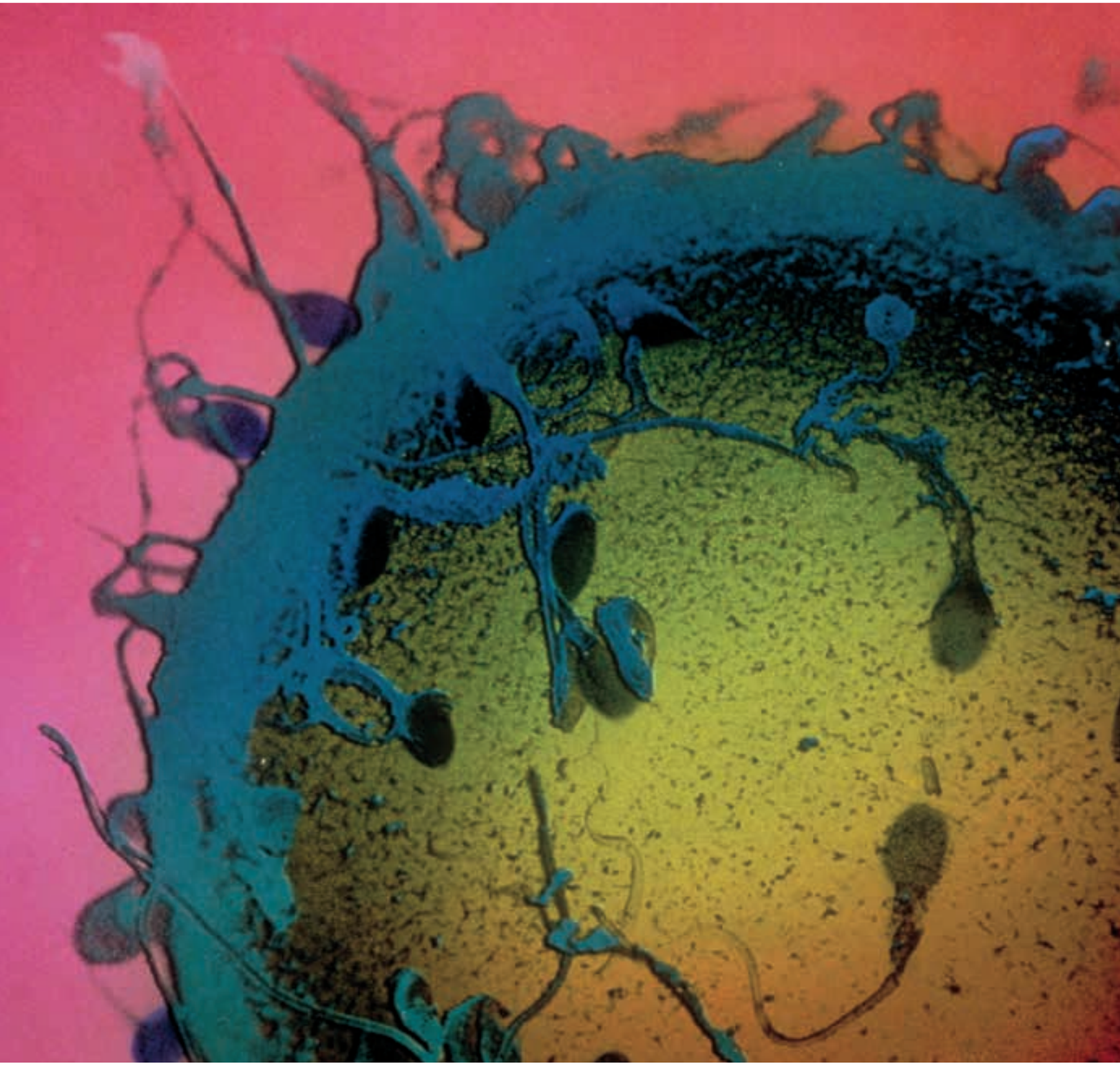
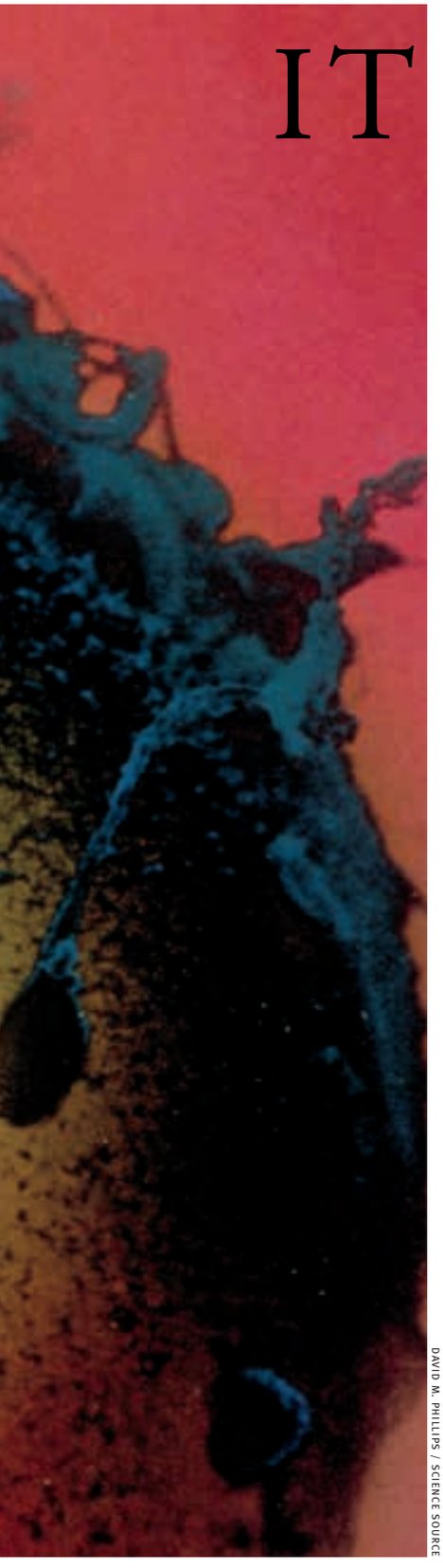
Explorations and revelations taking place in the medical school



Interacting reproductive proteins, from those of the eggs and sperm in humans (above) to those produced by certain sexually reproducing yeasts, evolve together. Nathan Clark is finding that the patterns of this process, called coevolution, could help scientists identify players in biochemical pathways much faster.



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IT TAKES TWO TO COEVOLVE

LIFE LESSONS FROM THE BIRDS AND THE FLIES

BY ALLISON A. CURLEY

You might expect that millions of years of evolution would have perfected the process of fertilization. Actually, the interacting sperm and egg proteins are still works in progress, says Pitt's Nathan Clark, a PhD assistant professor of computational and systems biology. "As the egg protein changes, the sperm protein that binds to it has to keep up." This process, where one adaptively compensates for changes in the other, is known as coevolution.

Clark's recent insights on proteins and their dance partners could be a boon for biomedicine. He's showing that by studying coevolution patterns, it may be possible to sleuth out previously unknown players in a given biochemical pathway—or perhaps even predict gene function.

In a study published in February 2013 in *Genetics*, Clark compared the rates of evolution between 40 different species (18 yeasts and 22 mammals), concentrating on genes that regulate a process of cell division, called meiosis, which is involved in reproduction.

In some yeast species, reproductive methods have evolved so that meiosis is no longer essential for survival. Clark showed that the evolutionary rates of meiosis-related genes whose proteins had direct physical interactions coevolved, accelerating in a parallel, correlated fashion, leading to a loss of the now-unnecessary meiosis-related DNA sequences. The same was true of the genes for proteins that participated in the same biochemical pathway, even though they didn't directly interact.

Recently, Clark's methods came in handy in a collaboration with Cornell University's Mariana Wolfner, who studies reproductive processes in fruit fly models. Wolfner was interested in studying a protein called "the sex peptide," which gives male *Drosophila melanogaster* an advantage in fertilization. The protein, which is passed from the male to the female along with his sperm, makes her uninterested in mating with other flies for several days.

Seven genes had already been implicated in this behavior. To see whether the team might be able to expand on the list, Clark took a look at the 600 genes expressed in fly reproductive tissue and created a prioritized list of genes whose evolutionary rates changed in parallel with the original seven. A postdoc in the Wolfner lab, Geoff Findlay, then performed a series of experiments to confirm that, of the 18 candidate genes Clark identified, six were indeed part of the pathway. In just two years, the team nearly doubled the number of known genes involved in this behavior.

"A gene's rate of change over time, and who it's changing with, can tell you a lot about its function," says Clark. This approach can be used to discover the function of virtually any protein, so "it's a general recipe we want to try to repeat," he adds. In the future, Clark hopes to create a publicly accessible database into which researchers can input their proteins of interest and receive a list of potential other members of the same pathway.

A related branch of Clark's research examines the process of coevolution experimentally. He's altering the structure of NUP84, a protein that forms a specialized tunnel, or nuclear pore, that allows molecules to be transported in and out of a cell's nucleus. Clark transplanted the NUP84 gene from one yeast species (the donor) into a second, closely related yeast species (the recipient), replacing its native copy of the gene. Even though the change was very small—the protein sequence differs by only 5 percent—the cells containing the foreign NUP84 gene grew much slower than those with the gene from their own species. This stunted growth occurs because the donor NUP84 has not coevolved with the recipient partner proteins, Clark explains. "We've essentially broken this adaptive [coevolution] process," he says. In addition, because the donor and recipient species are each other's closest relatives, the slower growth rate "tells us that the process of coevolution is going on constantly," he adds. ■