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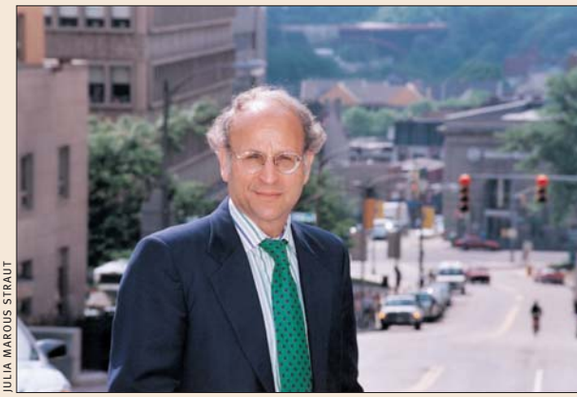
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JULIA MAROUS STRAUT

Some people, says Bloom, can see the mote in others' eyes but they can't see the beam in their own.

—James Joyce, *Ulysses*

In the "Cyclops" chapter, modeled after Homer's tale, Joyce's Bloom narrowly escapes from "the citizen," a blowhard nationalist he meets in a tavern. Although Bloom's nemesis has both eyes, he can't see more than one viewpoint. Here's another cyclops story—in this one, the characters can recognize complexity and keep their eyes wide open.

I was pleased to host recently Dr. Philip Beachy as one of our Laureate Lecture series speakers. Dr. Beachy is a professor of molecular biology at Johns Hopkins University, a Howard Hughes investigator, and a member of the National Academy of Sciences. He is known for revealing how the secreted proteins of the Hedgehog gene family mediate the proliferation and differentiation of embryonic cells. The peculiar Hedgehog name comes from Christiane Nüsslein-Volhard and Eric Wieschaus, who won the Nobel Prize for their classic mutant screens. In 1977, they identified a mutation in the fruit fly affecting its outer body layer. These scientists observed that the mutant fly embryo, with small spiky projections instead of orderly segments, resembles a hedgehog. Beachy cloned the fly's Hedgehog gene; he and others then went on to show that the gene is highly conserved in evolution and that the best-studied one, Sonic hedgehog (named for the video game character), regulates the organization of the midline structures of the brain in vertebrates. Mice with a disrupted Sonic gene are cyclopic. Mutations in the human version of the gene cause holoprosencephaly, a defect in which the embryonic forebrain doesn't divide into hemispheres and which can result in cyclopia. Dr. Beachy found that too much Hedgehog activity is equally bad: It's responsible for some cases of basal cell carcinoma (the most common human cancer) and the childhood brain tumor, medulloblastoma—both driven by excessive proliferation of precursor stem cells.

The plot thickens: In the 1960s, it was noted that sheep who graze on corn lily give birth to cyclopic lambs; the plant contains cyclopamine, a teratogen. Dr. Beachy found that this molecule blocks the Hedgehog signal and inhibits the growth of medulloblastoma as well as human prostate cancer cells transplanted in mice. (In fact, the level of Hedgehog gene activity may be helpful for prostate cancer prognosis: Metastatic prostate cancer cells have increased expression of the Hedgehog gene, and nonmetastatic cells do not.)

Several companies are now developing cyclopamine-like drugs as potential cancer therapies, and others are developing drugs that might augment Hedgehog expression. Given that Down syndrome patients have too few brain cells, it could be that treating a Down fetus in utero with such a drug might reverse some of the defects found in this syndrome. Such a drug might even help with myocardial ischemia. In any case, the moral of this story: Starting with an observation 30 years ago by the keenest of basic science eyes, a fruit-fly mutation now promises to illuminate the most fundamental mechanisms critical both to normal human development and to cancer, leading to possible remedies as well. What more could one ask of basic science, and what better definition of "translational research"?

Arthur S. Levine, MD
Senior Vice Chancellor for the Health Sciences
Dean, School of Medicine