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HHMI Professor's Phage-Hunters Strike Pay Dirt

A handful of Pittsburgh high school and college students, openly encouraged to dig in the dirt around their homes and schools by their teachers and professors, have isolated and characterized 30 viruses that infect bacteria. As a result of their foray into the world of scientific discovery, the students are now co-authors of an upcoming research article in a peer-reviewed scientific journal.

In the June 9, 2006, issue of *PLoS Genetics*, a research team headed by HHMI professor Graham Hatfull at the University of Pittsburgh reports that it has catalogued and characterized the genomes of 30 viruses called mycobacteriophages, which are viruses that infect bacteria. Phages, as they are known, are used by researchers to learn about the genetics of diseases such as tuberculosis and leprosy. Hatfull and colleagues report on 16 newly identified phages and provide a comparative analysis of those and 14 previously identified phages. HHMI investigator William R. Jacobs Jr. from Albert Einstein College of Medicine, is a co-author, as are 19 students from two high schools and the University of Pittsburgh.

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— Graham F. Hatfull

This is the second peer-reviewed publication from Hatfull's phage-hunting project, which breaches the traditional wall between science education and research by plunging high school and undergraduate students into research. The paper not only reveals the astonishing diversity of mycobacteriophages, it also shows that phage discovery and comparative genomics are an effective way to meld scientific discovery with education.

The separation of the missions of education and research is very damaging, said Hatfull. I really believe strongly that we need to bring them together. We need to engage students and make research opportunities broadly available if we are to prepare them for science in the future. Phage isolation and genomic analysis provides an engaging way to do that.

Phages are ubiquitous in nature. There are an estimated 10^{31} different phages—that's 10 with 30 zeroes after it—more than any other biological organisms. Under the microscope, they look remarkably similar, but at the genetic level, they demonstrate tremendous diversity.

One of the most striking characteristics of phages is their genomic structure, which resembles a mosaic. Groupings of genes appear as tiles in that mosaic, and each phage has a unique assemblage of tiles, giving them enormous genetic diversity. The goal of this paper was to sort all those genes and to characterize them into `phamilies,' or related genetic sequences, Hatfull explained.

The *PLoS Genetics* paper highlights the genetic diversity of phages. The researchers found 3,357 genes in the 30 phages studied, which they grouped into 1,536 phamilies. These genes were so diverse that more than half of the phamilies contained only a single gene, and 88 percent of the identified phage genes belonged to phamilies comprising three or fewer genes.

This genetic diversity gives the phages a robust capacity to recombine with genes in their bacterial host chromosomes, profoundly influencing the physiology of their hosts. Researchers believe that gene combinations between phage and host are responsible for the toxins of diseases such as cholera and diphtheria.

Jacobs, Hatfull's long-time collaborator and co-author on this paper, uses phages as a tool for understanding the genetics of tuberculosis (TB). The mosaic nature of these bacteriophages is just so surprising, Jacobs said. It's an orgy of DNA recombination. Every significant advance we've made in understanding TB—from how the BCG vaccine works to understanding multi-drug resistance—we've made because of phages.

Hatfull also uses phages to study TB and to develop tools for understanding mycobacterial genetics. But in addition to being important research tools for both scientists, phages are exciting educational tools, Hatfull said, especially when the education occurs within an active and productive research lab. Jacobs, who also opens his lab to high school and college student researchers, agreed. In fact, it was Jacobs who suggested to his twin sister, Deborah Jacobs-Sera, a high school biology teacher in Pittsburgh who was looking for an exciting science project, that her students might enjoy isolating phages. Jacobs referred her to Hatfull. She is now the coordinator for the University of Pittsburgh phage-hunting program.

Phage isolation and genomic analysis provides a unique, discovery-based educational platform because it places a strong emphasis on scientific discovery and project ownership, and it offers the opportunity to truly discover something new, Hatfull said. Phages, on average, are replete with new genes that no one has identified yet, he explained. There is a very high chance that students will discover something new.

For example, Andrew Hryckowian, 19, found a phage with a very large genome, including a gene that encodes transfer RNA (tRNA). These

molecules transport amino acids to the ribosome, the cell's protein-making machinery. Hryckowian found the new phage in the ground under a bush near the Cathedral of Learning on the University of Pittsburgh campus. He named it Catera, the name of his ex-girlfriend's dog.

Now entering his sophomore year at the University of Pittsburgh, Hryckowian joined Hatfull's phage-hunt when he was still in high school. During his own freshman year of college, Hryckowian mentored six high school students. This is his fourth summer of full-time work in Hatfull's lab.

"Working on the *PLoS Genetics* paper made me feel that I am actually contributing to the fund of scientific knowledge," Hryckowian said. "It's an opportunity not many undergraduates get."

The phage-hunting program also gives undergraduates the opportunity to develop as mentors to the high school students and to train others. Hatfull uses a program called *Entering Mentoring*, developed by another HHMI professor, Jo Handelsman, at the University of Wisconsin-Madison. HHMI professors are leading research scientists who have made a special commitment to improving undergraduate science education at research universities. *Entering Mentoring* trains students to teach by example, working as research partners with those they are training.

While his students hunt for phage diversity in the dirt of the greater Pittsburgh metropolitan area, Hatfull looks for diversity in the students participating in his program. We believe students learn more in a diverse environment and that not every student needs to be an A^+ wizard, Hatfull said. In fact, the educational benefits may be greatest for the kids who aren't A^+ students.