An international network of students in Hatfull’s SEA-PHAGES program has identified, analyzed, and categorized 15,000 bacteriophages. Three of those phages were used recently as part of a biomedical cocktail to save a British girl experiencing a life-threatening infection.
In October of 2017, a British teenager named Isabelle lay on her deathbed. The girl had been diagnosed with cystic fibrosis at a young age, and even though she’d recently undergone a successful double lung transplant to alleviate some of her more life-threatening symptoms, a bacterial infection had since taken over her body. Antibiotics failed to kill or even contain the microbes. With no traditional options left, Isabelle’s doctors reached out to Graham Hatfull.

You see, Hatfull is an expert on phages, viruses that hunt and destroy bacteria. Most people haven’t heard of phages, short for bacteriophages, but there are approximately 10 million trillion trillion of them on Earth, or about 10 million more than there are stars in the universe.

“Phage particles are the majority of all biological stuff on the planet,” says Hatfull, who is the Eberly Family Professor of Biotechnology at the University of Pittsburgh.

Under an electron microscope, phages look like a lunar lander crossed with a robot spider. And like other viruses, they cannot reproduce on their own. Instead, a phage must hijack a bacterial cell’s machinery to create copies of itself. It then multiplies inside the bacterium until there are so many that they burst out like candy from a smacked piñata. The bacterium dies as a result, while each new phage goes on the prowl for more hosts in which it can repeat the process.

Scientists have actually been using phages to combat bacterial infections since 1915, but the practice mostly fell out of favor with the rise of antibiotics. Isabelle’s doctors hoped to harness phage therapy to combat Isabelle’s infection.

Unfortunately, phages are what you might call picky eaters. Each one has evolved into a highly specialized predator of usually just one specific kind of prey. That’s why even though phages are everywhere, they can’t simply be grabbed from a puddle and injected into a sick person. Doctors need someone who can find precisely the right phage for the job.

That’s where Hatfull comes in. He and his team at Pitt are among the world’s leaders in collecting phages and learning what they do. They have also developed an international network of more than 150 schools that teach undergraduate students to process soil samples in the hopes of discovering new phages. Hatfull’s freezer library currently includes more than 15,000 phages, roughly two-thirds of which are closely related.

With samples of Isabelle’s bacteria in hand, Hatfull and his team were able to sift through their stores and isolate three candidates that might be able to go to war for the girl. One of these had been plucked out of a storm drain alongside the Heinz Memorial Chapel back in 2006 by a Pitt undergraduate named Tim Sampson. The other matches came from Rhode Island and South Africa. All three would go into the phage therapy cocktail as a way to prevent the bacteria from developing a resistance to any one phage.

Back in London, Isabelle’s liver had begun to fail, but the team in Pittsburgh still had one obstacle to overcome. Two of the matches were temperate phages, meaning they infect bacteria but do not kill them outright. Luckily, Hatfull’s lab had already experimented with a genetic modification to unleash a phage’s inner bacteria-bursting beast.

After tweaking the cocktail, performing a litany of safety tests to make sure it didn’t contain any toxins, and undergoing thorough regulatory approval, Hatfull’s team shipped the serum off to London.

Isabelle was the first person in the world to receive genetically modified phage therapy.

“Almost overnight things started to clear up and heal,” a grateful Jo Holdaway, Isabelle’s mother, told CNN about the case that captured worldwide attention. “It was just amazing.”

In six weeks, Isabelle’s infection nearly disappeared. Hatfull and his team published Isabelle’s groundbreaking case study in Nature Medicine in May 2019.

Today, more than a year since the June 2018 treatment, she still receives phage therapy on a regular basis, but her microbe levels are so low and her breathing so improved that she is no longer bedridden. Isabelle has returned to school and in many ways is living a normal, teenage life.

“This is a kid who we didn’t expect to survive,” says Hatfull. “That feels pretty amazing.”
The Human Genome Project gave us identities and locations of genes. Yet to really understand wellness and disease, we’ll need more than an address book. That’s why scientists are creating the equivalent of a Google Earth of the human body.

In 2018, the National Institutes of Health launched the Human BioMolecular Atlas Program (HuBMAP), which was tasked with creating a comprehensive atlas of our cells and tissues.

Tomes of new maps are in the works, using data from individual cell types and images of each cell in representative tissue samples. The end goal: a high-resolution, 3-D atlas of us, down to our most basic building blocks, which shows not only where cells are, but their many functions, as well. The atlas will render the tens of trillions of cells within human tissue, clarifying how these cells organize, specialize, and cooperate.

Jonathan Silverstein, chief research informatics officer and professor of biomedical informatics at the University of Pittsburgh, and Nicholas Nystrom, chief scientist at the Pittsburgh Supercomputing Center, are coprincipal investigators on HuBMAP’s infrastructure and engagement component. Silverstein also co-leads the steering committee of the HuBMAP Consortium with Michael Snyder at Stanford University.

HuBMAP collaborators elsewhere, at tissue mapping centers, will generate data about cell organization and variation within specific tissues and organs.

The Pittsburgh duo has developed the crucial framework to receive and manage data from the tissue mapping centers. High-quality, medically valuable data will come from advanced genomic sequencing, microscopy, and mass spectrometry for many different tissues, says Nystrom.

“When combined, these will provide a multimodal view of the tissues: physical appearance, genomic information, and protein expression, all at single-cell resolution. This is truly a medical first.”

Ziv Bar-Joseph, the FORE Systems Professor of Machine Learning and Computational Biology at Carnegie Mellon University, leads a separate center focused on the development of computational analysis methods for HuBMAP.

“Upon completion, the 3-D map has the potential to be a major tool over the next few decades, just as the Human Genome has been since its completion,” says Bar-Joseph. “This will be an amazing reference point in medicine and may lead to significant improvements in how we diagnose and treat disease.”
One hundred clicks. That's what it can take for a doctor using a typical hospital's electronic health record (EHR) just to order the right tests, check a history, and proceed with a patient's care.

A School of Medicine faculty member intends to change that. Among other things, Yalini Senathirajah's system would allow doctors to see the information they need at a glance, choosing which elements belong together on the screen.

MedWISE, an add-on to current EHRs, was designed by Senathirajah, a PhD associate professor of biomedical informatics. With the system now in beta phase, she's testing it to see if the approach helps physicians get the information they need without the cognitive load and potential for errors associated with most modern EHRs. And Senathirajah is looking for more recruits.

“I'm really keen to see: What will physicians do with it? I'm interested to see patterns and if they think of uses we didn't think of,” she says.

“If the [EHR] system can be adapted by physicians to meet their needs, in public health emergencies it could be rapidly adapted to create new solutions without waiting three months for the IT department to provide a solution.”

Senathirajah came up with the idea while working on her PhD in health care informatics at Columbia University. She was inspired by her own experience as a technical advisor for a large academic medical center. In that role, she got to see up close how EHRs don't quite go far enough to help physicians make timely and efficient medical decisions.

Here's how MedWISE works: Doctors can assemble information from a system's existing EHR into tiles, juxtaposing them on the same screen, and creating new elements. For example, physicians can create a calculator tile if the case requires, and even color-code the elements, or create specialty-specific items.

For example, as she's seen in beta users, “You [might] put all the important things in red and put them on the right,” she says. “And then pull up brain scans and code them blue.”

So far, the approach has been tried using data from the NewYork–Presbyterian Hospital. Senathirajah and colleagues have published indirect evidence of cognitive load reduction. Right now, the focus is testing the safety, efficiency, and other cognitive effects of the approach, and potentially using those results to develop a case for adoption by medical systems.

“MedWISE allows sharing configurations,” she says. This could help physicians save time—if the next provider for that patient thinks the same way. And what if that clinician doesn't?

Will that user change the configuration? If not, could that cause medical errors? Senathirajah is now running a study of 66 physicians to find out.

Another study—of 32 clinicians, including physicians, nurse practitioners, and physician assistants—will compare MedWISE to usual EHR configurations to look at how long it takes users to complete specific tasks. Colleagues at Columbia University will participate. Senathirajah is looking forward to bringing her Pitt colleagues into the research.

“I'm lucky to have colleagues and students here that are so interested in solving this problem,” she says.

“One reason I took this job is because my boss and others have been tremendously supportive and understood what I'm trying to do.”