INFECTIONOUS DISEASE

New drugs turn the tables on pathogens

BY NICK HOUTMAN

Carnivores eat their prey from the outside, author David Quammen writes in his 2012 book Spillover. Pathogens attack from within and are no less deadly. They enter our bodies unseen when we breathe, have sex, take a drink of water or just walk in the woods.

And they are relentlessly opportunistic. Pathogens that cause about six out of 10 human diseases — including AIDS, influenza, cholera, malaria, tuberculosis and Ebola — infect animals such as birds, bats, cattle, monkeys, camels and other species. These microbes bring humans and animals together in a deadly exchange driven in part by shifting environmental conditions. Through a global initiative known as One Health, veterinary and human health organizations are coordinating research and sharing results. They are tracking pathogens wherever they go.

Researchers at Oregon State University take a multipronged approach to these diseases. They are delving into the social and historical dimensions of disease transmission and medical science. In the face of growing resistance to antibiotics, they are developing new drugs, including antivirals. They are helping public-health agencies get the most from vaccination campaigns and efforts to combat outbreaks.

While the nearly complete eradication of smallpox, polio and other diseases stands as a triumph of medicine and science, new threats are emerging. For example, climate change raises the possibility that malaria, eradicated in the United States in the early 1950s, could come back. And as the footprint of human development expands, pathogens such as the bacteria that cause Lyme disease proliferate along with their preferred host, the blacklegged tick.

“It’s a race that humans cannot win,” says Luiz Bermudez, Oregon State professor of Veterinary Medicine. “Microbes grow too fast. They modify too fast. There are billions of them.” Our best chance, he says, is to disarm them without promoting resistance.
Infectious disease is a kind of natural mortar, binding one creature to another, one species to another, within the elaborate biophysical edifices we call ecosystems.”

— David Quammen, Spillover: Animal Infections and the Next Human Pandemic

Inside Job

Researchers target microbial machinery

As Patrick Iversen tells it, the push for a new Ebola drug got started with a kick from a laboratory mouse. On a Friday in 2004, the senior vice president for research at AVI BioPharma (now Sarepta Therapeutics) was having lunch with Alan Timmins, AVI’s president, when Iversen received a call from a colleague at the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) in Maryland. A lab worker was injecting Ebola into a mouse when the animal kicked and sent the virus-filled needle into the researcher’s double-gloved hand.

Iversen, now a research professor at Oregon State University, had just returned from USAMRIID. He had talked up AVI’s success in treating two deadly viral infections: West Nile in penguins at the Milwaukee Zoo and feline calicivirus in Eugene and Atlanta.

“It takes only one particle (of Ebola virus) for this woman to be killed,” Iversen says the caller told him. “We’re going to try everything. What can you do?”

Iversen turned to Timmins. “I asked him, ‘What do you think? Is this something we can try?’ He made the decision immediately. ‘Yeah, let’s do it,’” Iversen recalls.

“The whole company became Ebola for the weekend in 24-hour shifts,” he explains. “We had designed the compound by 2:30 or 3 and (sent it) over to the chemistry group by 4. They started assembling their reagents, and that evening they...
were synthesizing it. On Monday we got authorization (from the U.S. Food and Drug Administration) that we could use this in the patient.”

Ultimately, the lab worker didn’t test positive for Ebola, so doctors didn’t administer the drug. However, the three days in which scientists created the compound — in contrast to the decade or more it normally takes to develop a new pharmaceutical — shows the power of a biomedical technology that owes much to Corvallis-area scientists.

AVI Biopharma emerged from another company, Antivirals, which was founded to develop technology created by OSU professors Jim Summerton and Dwight Weller. Today Summerton runs Gene Tools LLC in Philomath, which also grew out of Antivirals.

At the heart of these efforts are advances in the ability to probe the genes and proteins that make infectious agents such as Ebola, influenza, HIV, tuberculosis and malaria so deadly. By knowing how bacteria and viruses replicate, navigate through the human body and enter a cell, researchers are learning to outsmart and disarm the invaders.

Worldwide Killers

Tuberculosis and malaria kill more than 2 million people a year, mostly in low-income countries. Although death rates have been falling for decades, progress is slowing. Frontline antibiotics are losing their effectiveness. According to the World Health Organization, about 500,000 cases of multidrug resistant TB were reported in 2013. Resistance to antimalarial drugs has been growing since the 1970s.

These trends worry Taifo Mahmud, a medicinal chemist in the Oregon State College of Pharmacy. The son of an Indonesian doctor who treated people with TB and malaria, Mahmud is developing new drugs by turning to the bacteria that produce them. Since they are made in nature, such compounds are known as “natural products.” In his lab, colorful microbial colonies produce the compounds that he pits against TB and malaria pathogens.

To find a new malaria treatment, Mahmud is focusing on pactamycin, a powerful broad-spectrum antibiotic that is so toxic to human cells that it is unfit for medical use. In search of a way to modify pactamycin, Mahmud deleted genes from the bacteria that make the compound. He has shown that, in cell culture, the altered form of the drug retains its potency against the malarial parasite but is about 30 times less toxic to human cells. Additional tests are underway.

For tuberculosis, Mahmud turns to rifampin, a TB drug-of-choice since the 1960s. By throwing a switch in its genes, Mycobacterium tuberculosis, the pathogen that causes the disease, has learned to shrug off rifampin like a bad joke. So Mahmud and his team have re-engineered the bacteria that make the
Running the Numbers
Modelers fight disease with mathematics

Whenever he can, Jan Medlock relies on official sources. He gathers data on infectious disease from the World Health Organization, the U.S. Centers for Disease Control and Prevention (CDC) and government health ministries. But last summer, the assistant professor in the College of Veterinary Medicine at Oregon State found himself turning to the fount of family photos and puppy videos: Facebook. In Liberia, the Ministry of Health and Social Welfare was reporting Ebola cases on the global social network.

With colleagues at Yale University, Medlock assembled data from Facebook posts, the 2008 Liberian housing census and the previous Ebola outbreak in the Democratic Republic of the Congo. The researchers scoured medical literature for data on transmission factors such as how many people, on average, are likely to be infected by one sick person. Finally, they calculated the risks of catching Ebola in three different circumstances: communities, hospitals and funerals.

The findings were stark. The study found that a healthy person was about 15,000 times more likely to catch Ebola at a funeral than in the general population, says Medlock. “To stem Ebola transmission in Liberia,” the scientists wrote in the journal Science, “it is imperative to simultaneously restrict traditional burials, which are effectively serving as super-spreader events.”

Medlock sees a need for household level surveys to increase the accuracy of future disease projections. “Our tools fit the general patterns of outbreaks well,” he says, “but they are quite bad at getting the numbers right.”

Dead Giveaway
Even among resistant microbes, Neisseria gonorrhoeae is a star. It has thwarted a host of antibiotics including sulfas, penicillin, tetracycline and fluoroquinolones. About 106 million new cases of this sexually transmitted disease are reported around the globe every year, and it is the second most commonly reported infectious disease in the United States. For treatment, only compound, essentially giving it a new punch line. In cell culture experiments, they found that the new drug kills resistant TB bacteria. The M.J. Murdock Charitable Trust and the Medical Research Foundation of Oregon provided funding.

A new tuberculosis treatment is also under study in Luis Bermudez’s lab in the College of Veterinary Medicine. With support from the National Institutes of Health, he has confirmed that a compound never before used as an antibiotic kills M. tuberculosis cells. However, in what could be a setback, he also found that it triggers resistance and enables some bacteria to survive.

Bermudez and his team have identified an enzyme that plays a key role in this process. In cell cultures, they administer the drug together with an enzyme inhibitor. As a result, they have cut the time it takes to kill TB cells from six days to two. Since treating TB now takes as long as six months, faster recovery could cut costs and curtail the development of resistance to new drugs.
compounds known as cephalosporins are still effective, but their days are numbered. Bacterial strains resistant to these antimicrobials are beginning to appear.

Among the consequences of infection are pelvic inflammatory disease, ectopic pregnancy and infertility. Furthermore, repeated infection facilitates the acquisition and spread of HIV.

In her lab in the College of Pharmacy, Aleksandra Sikora is looking for new ways to outwit *N. gonorrhoeae*. “Unfortunately, no gonorrhea vaccine exists and surprisingly little work has been done to develop such a vaccine,” Sikora says.

Sikora’s group is the first to use the science of proteomics — the comprehensive analysis of protein composition and structure — to identify potential targets for gonorrhea vaccines. In the journal *Molecular and Cellular Proteomics*, Sikora and colleagues at Seattle’s Fred Hutchinson Cancer Research Center reported the discovery of novel proteins in the bacterial cell envelope and in the naturally released vesicles — small pouches within the cells.

Sikora also collaborates with Ann Jerse, a professor at the Uniformed Services University in Bethesda, Maryland, who has developed a mouse genital tract infection model for testing candidate vaccines.

**Spoils of War**

In 2003, when a multidrug-resistant pathogen started showing up in U.S. troops wounded in Iraq, it was nicknamed “Iraqibacter.” Its scientific name — *Acinetobacter baumannii* — doesn’t exactly roll off the tongue.

Soldiers were coming down with hard-to-treat infections in field hospitals. Major facilities such as the Walter Reed National Military Medical Center in Washington, D.C., weren’t spared. In 2009, the Public Broadcasting Service (PBS) reported that *A. baumannii* infections affected as many as 20 percent of all wounded soldiers in military hospitals. Health authorities referred to Iraqibacter as a “superbug.”

So when Oregon State microbiologist Bruce Geller was considering a practical target for a new approach to pathogen control, this one seemed like a good choice. Geller had been collaborating with Patrick Iversen and other researchers at AVI Biopharma on a gene-based treatment for bacterial diseases. Working with *E. coli* as a model organism, the researchers succeeded in delivering a synthetic compound known as a “Morpholino oligomer” — a string of genetic building blocks designed to bind to specific sequences of mRNA, a major component of cells — into *E. coli* and killing them. Morpholinos work by blocking the expression of genes that are necessary for microbes to survive.

Experiments with *Acinetobacter* infected mice show promise. In 2013, Geller and co-authors at Sarepta Therapeutics and the University of Texas reported in *The Journal of Infectious Diseases* that treatment with a Morpholino tailored to *Acinetobacter* genes increased the survival of infected mice. Moreover, as doses were raised, symptoms of inflammation decreased and survival rates grew accordingly.

A significant challenge, says Geller, was finding a way to deliver Morpholinos into the cell. As antibiotic molecules go, Morpholinos are large. Hong Moulton, director of drug delivery research and development at AVI, solved that...
Infectious diseases are not equal-opportunity illnesses. Much depends on location, income and access to clean water, medical care and public health services. For example, mosquito control is still a bulwark against malaria and yellow fever. Historically, trade routes were highways for pathogens such as Vibrio cholera and Yersinia pestis, the bacteria that cause cholera and plague respectively.

The close relationship between geography and disease is revealed in a new interactive atlas produced by Oregon State University students. The Atlas of Infectious Diseases combines global data on wealth, water, health care and historical and modern diseases such as tuberculosis, malaria, AIDS, polio and Ebola.

“Geography introduces a multiscale analysis of the distribution and spread of infectious diseases between individuals and across regions,” says Brooke Marston, one of the authors and a graduate student in the College of Earth, Ocean, and Atmospheric Sciences. Marston was one of 19 students who produced the atlas in a computer-assisted cartography course taught by Assistant Professor Bernhard Jenny.

The biggest challenge, she adds, was getting access to data. “There was not always a wealth of data readily available. Additionally, privacy laws may require data to be aggregated and stripped of individual identifiers, making it difficult to visualize data on a finer scale.”

The atlas was produced for the iPad and can be downloaded free from the iBooks Store or the OSU Cartography and Geovisualization Group’s website, cartography.oregonstate.edu.

A non-interactive version for desktop computers and other tablets is also available.

The atlas received the 2014 New Mapmaker Award from the British Cartographic Society and the National Geographic Society and the 2014 NACIS (North American Cartographic Information Society) Student Dynamic Map Competition Award for Best Narrative Map.