their standards are equivalent, which does not necessarily mean making all regulations identical, as many people assume. If regulations are harmonized in some instances, he points out, citizens would be able to push for the higher standard — not the lower — to be adopted.

Greater clarity on how medicines will be treated by regulators would be a boon for pharmaceutical research, says Richard Bergström, director-general of the European Federation of Pharmaceutical Industries and Associations in Brussels. It could also mean that drugs reach patients earlier, because companies would no longer have to apply separately to US and EU regulators, a process that can involve costly and time-consuming tests, especially for paediatric medicines. "I'm both surprised and quite frustrated by the debate around TTIP," he says.

"TTIP is set to change the way in which scientific cooperation is set to take place."

Another fear surrounding the trade agreements is that if they are ratified they will include a legal framework known as an investor-to-state dispute resolution mechanism, which would allow companies to take governments to court and overturn legislation. A company could thus limit a government's ability to regulate a certain chemical on health grounds if that were seen as an unreasonable restriction of the company's trade as laid out in the treaty. Objectors to the treaties fear that a dispute provision would also discourage governments from passing strict legislation in the first place.

The history of the North American Free Trade Agreement (NAFTA) and other such agreements is littered with such cases, says Pfotenhauer. The pharmaceutical firm Eli Lilly is currently suing Canada under NAFTA after the government invalidated patents on two of the company's drugs in an argument over interpretation of clinical-trial data. Companies have also tried to use NAFTA to force Canada to allow toxic-waste exports and to include an additive in petrol that the nation's regulators claimed was dangerous.

These cases revolved around the interpretation of scientific knowledge, notes Pfotenhauer. Indeed, one thing that NGOs, lawyers and governments agree on is that scientists should care about the trade deals. "TTIP is set to change the way in which scientific cooperation is set to take place across the Atlantic," says Alemanno.

And there may be little point in fighting the deals. Against a background of gloom and pro-free-trade governments, says Alemanno, even if this particular trade negotiation breaks down, as a philosophy, "TTIP is here to stay". ■ SEE EDITORIAL P.393

DRUG DEVELOPMENT

Bacterial arms race revs up

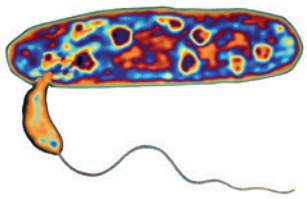
With antibiotic resistance on the rise, researchers are looking for new ways to treat infections.

BY SARA REARDON

More than eight decades have passed since Alexander Fleming's discovery of a fungus that produced penicillin — a breakthrough that ultimately spawned today's multibillion-dollar antibiotics industry. Researchers are now looking to nature with renewed vigour for other ways of fighting infection.

Few new antibiotics are in development, and overuse of existing ones has created resistant strains of deadly bacteria. "We need a change from what we have," says Stephen Baker, head of medicinal chemistry for antibacterials at GlaxoSmithKline in Collegeville, Pennsylvania.

Baker will talk about some of the alternatives to antibiotics on 2 June at the American Society for Microbiology's annual meeting in New Orleans, Louisiana. Here are a few of the therapies that scientists are exploring.



ALFRED PASIEKA/GETTY

***Bdellovibrio bacteriovorus* preys on other bacteria.**

PREDATORY BACTERIA

Bacteria cause infection, but some can also fight it by preying on fellow microbes. Several researchers are beginning to test these predatory bacteria in animal models and cell cultures.

The best-known species, *Bdellovibrio bacteriovorus*, is found in soil. It attacks prey bacteria by embedding itself between the host's inner and outer cell membranes, and begins to grow filaments and replicate. "It's like going into a restaurant, locking the door and starting to munch away," says Daniel Kadouri, a bacteriologist at Rutgers University in Newark, New Jersey. The host bacterium eventually explodes and releases more *B. bacteriovorus* into the environment.

Kadouri and others are also studying the therapeutic potential of the predatory bacterium *Micavibrio aeruginosavorus*. And a team has engineered the gut bacterium *Escherichia coli* to produce peptides that kill *Pseudomonas aeruginosa*, a microbe that causes pneumonia.

This preliminary research is attracting attention. The Pathogen Predators programme of the US Defense Advanced Research Projects Agency, which aims to treat soldiers who contract infections on the battlefield, announced nearly US$16 million in research grants this week to groups studying predatory bacteria.

ANTIMICROBIAL PEPTIDES

Plants, animals and fungi have vastly different immune systems, but all make peptides — small proteins — that destroy bacteria. Peptides from creatures such as amphibians and reptiles, which are unusually resistant to infection, could yield new therapeutics.

Peptides with antibacterial activity have been isolated from frogs, alligators and cobras, among others, and some seem to be effective in epithelial cell cultures and at healing wounds in mice. These peptides can be modified to increase their potency, and several are

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JIM ABERNETHY/NATIONAL GEOGRAPHIC CREATIVE

Peptides produced by the American alligator could add to the arsenal of antibacterials.

in clinical trials. One, called pexiganan, based on a peptide from frog skin, is now in phase III clinical trials to treat diabetic foot ulcers.

But synthesizing such molecules can be expensive, a hurdle that scientists must overcome to bring new peptide drugs to market.

PHAGES

Of all the alternatives to antibiotics, phages — viruses that attack bacteria — have been used the longest in the clinic. Scientists in the Soviet Union began developing phage therapies in the 1920s, and former Soviet countries continue the tradition.

Phages have several advantages over antibiotics. Each type attacks only one type of bacterium, so treatments leave harmless (or beneficial) bacteria unscathed. And because phages are abundant in nature, researchers have ready replacements for any therapeutic strain that bacteria evolve to resist.

Mzia Kutateladze, who heads the scientific council at the Eliava Institute in Tblisi, Georgia, says that antibiotic resistance is driving more Western patients to phage-therapy clinics in Eastern Europe. The US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, now lists phages as a research priority for addressing the antibiotic crisis. A clinical trial of a phage treatment for infections associated with burns is planned by a consortium of European centres to start this summer.

GENE-EDITING ENZYMES

CRISPR, a gene-editing technique that has taken the scientific world by storm, is based on a strategy that many bacteria use to protect themselves against phages. Researchers are turning that system back on itself to make bacteria kill themselves.

Normally, the bacteria detect and destroy invaders such as phages by generating a short RNA sequence that matches a specific genetic sequence in the foreign body. This RNA snippet guides an enzyme called Cas9 to kill the invader by cutting its DNA.

Scientists are now designing CRISPR sequences that target genomes of specific bacteria, and some are aiming their CRISPR kill switches at the bacterial genes that confer antibiotic resistance.

METALS

Metals such as copper and silver are the oldest antimicrobials. They were favoured by Hippocrates in the fourth century BC as a treatment for wounds, and were used even earlier by ancient Persian kings to disinfect food and water. Only now are researchers beginning to understand how metals kill bacteria.

Some groups are exploring the use of metal nanoparticles as antimicrobial treatments, although little research has been done in people. Because metals accumulate in the body and can be highly toxic, their use may be restricted mostly to topical ointments for skin infections.

An exception is gallium, which is toxic to bacteria that mistake it for iron, but is safe enough in people to be tested as an intravenous treatment for lung infections. This summer, researchers at the University of Washington in Seattle will begin a phase II clinical trial of gallium in 120 patients with cystic fibrosis. Pilot studies found that the metal was moderately successful at breaking down microbial biofilms in the lungs and improving patients' breathing. ■