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Into the deep – antibiotics from the seabed

Decades of antibiotic use and overuse of have driven the evolution of a new generation of resistant superbugs. Because investing in antimicrobials usually brings a poor return, however, drug developers have not come up with replacement antibiotics for decades. Now experts are sounding the alarm. If nothing is done, infections that were once easy to treat could again become major killers in the next twenty years. Researchers now hope that help could come from the depths of the sea.

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ANTIBIOTIC RESISTANCE

The real treasures of the deep

We are under fire from a health threat we thought we had mastered long ago. Decades of antibiotics use have fueled resistance in bacteria that were once easily killed by them. Most pharmaceuticals firms largely abandoned the search for new antimicrobial compounds years ago because it was unprofitable, and that has now left a dangerous gap in our medical arsenal. In an attempt to fill it, governments across the globe are sponsoring an array of initiatives to identify novel antibiotics. Two of them kicked off in February as part of the EU Action Plan. The €223.7m programme sponsored by the Innovative Medicines Initiative (IMI) is seeking to support and promote the clinical development of novel Phase III antibiotics with the help Big Pharma. At the same time, marine researchers from the PharmaSea consortium will be plumbing the depths of the world’s oceans to search for antibacterial substances that have evolved in one of the planet’s most extreme environments. With equipment normally used by the salvage industry, PharmaSea’s microbiologists will bring up organisms from thousands of meters below the surface of the sea and test them for promising new drug leads.

“Antimicrobial resistance represents a major threat to public health worldwide,” says IMI Executive Director Michel Goldman. “Developing new antibiotics is challenging, but by bringing together experts from the pharmaceutical industry, academia, and hospitals, these new projects will give a fresh impetus to the search for new weapons to fight the drug-resistant pathogens that have already killed so many in Europe and elsewhere.”

It’s a little-known fact that infections involving multi-drug resistant (MDR) pathogens already kill around 25,000 people annually in the EU, and that number could explode in the next decade if novel antibiotics are not developed to treat them. Commercial development of new antimicrobial substances peaked during the 1990s, and has fallen dramatically in the last decade and a half. From 2000–2010, the numbers of new substances approved for market hovered just over levels from the 1950s. Currently around 80 antibiotic substances are marketed worldwide, but a completely new one hasn’t been registered since 2003, and no new class of substances has been introduced since the 1980s.

Health experts warn that if this trend continues unchecked, within the next twenty years we could enter an era like that before the advent of antibiotics – when straightforward bacterial infections were untreatable, and often deadly. The UK’s chief medical officer, Prof. Dame Sally Davies, has said the seriousness of the problem is at least as great as that posed by terrorism and climate change. “It’s clear that we might not ever see global warming,” she told members of the British parliament in late January. “The apocalyptic scenario is that when I need a new hip in 20 years, I’ll die from a routine infection because we’ve run out of antibiotics.”

Weird and wonderful chemicals

Under the FP7 programme, the European Commission is currently funding a range of projects aimed at identifying and exploiting useful molecules produced in the sea (see table). Marine organisms – especially those that live over 2,000 meters below the surface – are a very promising resource in the search for new antibiotics and new bioactive compounds. Because they have evolved under extreme conditions, many of the chemicals deep-sea organisms produce could prove highly effective at destroying bacteria found in less demanding environments.

This fall, the EU-sponsored €9.46m PharmaSea project will begin mining the ocean floor for deep-sea sponges and bacteria, with the long-range goal of evaluating their potential as novel drug leads. “By choosing deep and cold marine environments we hope to tap novel diversity not seen before,” lead scientist Marcel Jaspars from the Univer-
Deep ocean trenches are islands of diversity in which evolution may have progressed differently.” Coordinator Camila Esguerra from the University of Leuven in Belgium emphasised that “PharmaSea will not only be exploring new territory at the bottom of the oceans, but also new areas in ‘chemical space’ … we’ll be testing many unique chemical compounds from these marine samples that have literally never seen the light of day.”

Very little is known about the species that inhabit the crushing darkness of deep-sea trenches and arctic seas. PharmaSea’s international team – which includes partners from China, Chile, Costa Rica, New Zealand and South Africa – will employ strategies used in the salvage industry to carry out sampling and collect sediment. The scientists will then attempt to grow unique bacteria and fungi extracted from the sediment and isolate novel molecules for pharmacological testing. “We will use selective isolation protocols, paying special attention to the nutrient environment where the sediments were collected,” says Jaspars. “The use of genome scanning will be vital to assess the biosynthetic potential of the organisms and select only those which produce novel chemistry.”

The first field tests are to be carried out next autumn in the Atacama Trench in the Eastern Pacific Ocean off the coast of Chile and Peru. The team will also be searching the Arctic waters off Norway and the Antarctic, and deep trenches will be accessed off New Zealand and China. “We have assembled a team of 24 partners in the EU and worldwide – from academia, research institutes, not for profit organisations and small companies – with expertise in a diverse range of fields to work together to solve problems,” says Jaspars.

### Addressing fundamental flaws

One of the biggest of those problems involves markets. With cheap, effective antibiotics readily available, drugmakers have had little incentive to develop new ones. “Cooperation between universities and the pharma industry doesn’t have the right dynamic in the field,” complains Jörg Hacker, the President of Leopoldina, the German National Academy of Sciences, which has published an eight-point action plan for addressing the problem of MDR pathogens.

One of the biggest problems from the developers’ point of view is low profit margins. Until now, a patient who completed a 1-2 week course of antibiotics was generally cured. For pharma companies, however, drugs that have to be taken on a regular basis for longer periods of time are a more interesting proposition, because they provide manufacturers with better chances to recoup the huge development investments incurred on the road to approval. Hacker and other experts also say that rules involving market approval for new drugs – especially the one stating that a new medicine has to be superior to those already available – should not apply to the development of new antimicrobials. Because the topic is one that affects society as a whole, they say, governments have to create frameworks that increase chances of approval and lessen risk for the developers involved.

### Changing baseline expectations

Like PharmaSea, the EU Action Plan is aimed at fostering an unprecedented partnership between industry, academia and biotech organisations. Through its antimicrobial resistance programme “New Drugs 4 Bad Bugs” (ND4BB), the IMI-initiative launched two other new projects in early February. With over €194m in funding, COMBACTE (Combatting Bacterial Resistance in Europe) is aimed at creating a comprehensive clinical research agenda that includes the entire research community rather than just drug developers. TRANSLOCATION (€29.3m) will be specifically examining the molecular basis of bacterial cell wall permeability. In other words, it will look at the best pathways for getting antibiotics into microorganisms – especially the drug-resistant Gram-negative bacteria like E. coli and K. pneumoniae that are responsible for around two-thirds of the deaths caused by MDR pathogen infections. Along with PharmaSea, those programmes are seeking to redefine the ways in which academics and the industry interact through bypassing traditional ‘fee for service’ models. The EU programmes recognise that the road to obtaining alternative antibiotics can no longer be just a commercial endeavour.