

To treat or to tolerate pathogens, that is the question

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Xenopus laevis, from Chimanimani, Manicaland, Zimbabwe. Credit: [Brian Gratwicke](#), CC BY 2.0

Why do some people seem to never get sick while others consistently fall prey to viruses and bacteria? How can the spouse of a sick person avoid

catching their partner's bug despite sleeping next to them every night? Questions like these have become top-of-mind for many people during the COVID-19 pandemic, and scientists are now a big step closer to answering them thanks to some aquatic helpers: tadpoles.

Researchers at the Wyss Institute for Biologically Inspired Engineering at Harvard University have discovered genetic and biological mechanisms that enhance disease tolerance—the ability of cells and tissues to resist damage in the presence of invading pathogens—in developing tadpoles of *Xenopus laevis* frogs, and identified drugs that can keep the tadpoles alive even in the presence of lethal bacteria. Many of the same mechanisms are also found in mammals, suggesting that infections in humans and other animals could one day be treated by increasing their tolerance to pathogens.

"The standard approach to treating infections for the last 75 years has been to focus on killing the pathogen, but the overuse of antibiotics in livestock and in humans has led to the emergence of antibiotic-resistant bacteria that we are having a harder and harder time killing. Our research has shown that focusing on modifying a host's response to a pathogen rather than killing the pathogen itself could be an effective way to prevent death and disease without exacerbating the problem of antibiotic resistance," said first author Megan Sperry, Ph.D., a Postdoctoral Fellow at the Wyss Institute who is co-mentored by Wyss faculty members Michael Levin, Ph.D. and Donald Ingber, M.D., Ph.D.

The research is published today in *Advanced Science*.

Mapping the tadpole tolerance network

The phenomenon of some hosts being tolerant of infectious pathogens that should sicken them has been well-documented in science over the last few decades. Mice, for example, can harbor pneumonia-causing

Pneumococcus bacteria in their nasal passages without displaying signs of illness, and African and Asian monkeys are known to be less susceptible to certain pathogens than humans and our close ape relatives.

Research into the biology of disease tolerance has found that it is associated with the activation of stress responses that are normally induced by a low level of oxygen (hypoxia). These cellular responses reprogram T cells, which reduces the amount of inflammation they cause, and also impact the movement of [metal ions](#), which are crucial for bacterial survival.

As part of the Wyss Institute's ongoing quest to identify drugs that could replicate these biological processes and induce tolerance in humans, Sperry and her team wanted to see if they could use a combination of computational techniques and hands-on experiments to tease out the genes and molecular pathways that control tolerance in *Xenopus* frogs, and then find existing drugs that could activate those pathways and induce a state of tolerance against pathogens.

They chose to use *Xenopus* frog embryos for their studies because these embryos are easy to grow and analyze in large numbers and are known to display natural tolerance to high loads of certain types of bacteria. They exposed the embryos to six different species of pathogenic bacteria, and then analyzed the animals' [gene expression](#) patterns following infection. Embryos that encountered the more aggressive species *Aeromonas hydrophila* and *Pseudomonas aeruginosa* displayed visible changes in their physical development at 52 hours post-infection and widespread modifications to their gene expression patterns one day after infection, reflecting the animals' physiological responses to the pathogens.

The other four species caused no visible change in the embryos, which at first suggested that the animals weren't reacting to the pathogens. But the [genetic analysis](#) told a different story. While two of the species, *S.*

aureus and *S. pneumoniae*, caused very few genetic changes in the embryos' gene expression profiles, the species *Acinetobacter baumannii* and *Klebsiella pneumoniae* caused significant changes in a set of 20 genes that had been unchanged during infection with the more aggressive bacteria. These genetic changes seemed to correlate with a positive impact on the health of the developing [frogs](#), implying that they could be involved in the animals' tolerance response.

The researchers used a computational approach to map *Xenopus* genes that underwent significant change to their corresponding genes in humans, and analyzed how those genes interact with each other by organizing them into "gene networks." They found that the embryos that tolerated *A. baumannii* and *K. pneumoniae* had significant shifts in their gene networks that were distinct from the shifts seen in embryos that succumbed to infection with *A. hydrophila* and *P. aeruginosa*.

One particular gene, HNF4A, was highly upregulated in the tolerant embryos, and was connected to several genes that are involved in transporting metal ions and increasing oxygen availability—both processes that have been previously linked to disease tolerance. HNF4A also helps maintain the circadian rhythm, and the scientists found that flipping the embryos' light cycle increased tolerance against *A. hydrophila* infection, raising the intriguing possibility that modulating circadian rhythms could impact an organism's response to infection.

"It was really exciting to see that pathogen tolerance seems to be modulated by multiple coordinated [biological processes](#)—hypoxia, metal ion transport, and circadian rhythm—because it might be possible to develop a whole class of drugs that simultaneously target multiple pathways to help make organisms more resistant to damage by infection while avoiding undesirable side effects," said co-author Richard Novak, Ph.D., a former Lead Staff Engineer at the Wyss Institute who is now co-founder and CEO of Unravel Biosciences.

Treat the body, not the bug

Armed with these promising results, Sperry, Novak, and their team set out to see if they could find any such drugs. First, they compared the gene expression signature they'd identified in the tolerant *Xenopus* embryos to existing data from mice and primates that had been infected with bacteria against which they were tolerant. They found that the [gene networks](#) in tolerant *Xenopus* embryos shared key overlaps with those found in tolerant mice and primates, and that twelve genes were common across all the species. Among those genes were several that are involved in a process called nuclear factor kappa B (NF- κ B) signaling, which regulates inflammation responses to infection, as well as metal ion transport and cellular hypoxia responses.

Confident that the *Xenopus* tolerance genes were a good proxy for aspects of tolerance in mammals, they then screened more than 30 pharmaceutical drugs that are known to impact metal ion transport or hypoxia by administering them to *Xenopus* embryos that were infected with *A. hydrophila*. Three drugs substantially increased embryo survival despite the presence of a pathogen that should have killed them: deferoxamine, an FDA-approved drug that binds to iron and aluminum ions; L-mimosine, which binds to iron and zinc; and hydralazine, which binds to metal ions and also dilates blood vessels.

Because metal ion transport and hypoxia pathways are known to be interconnected, the researchers had a hunch that these metal scavenging drugs were stabilizing a biological protein called HIF-1 α . HIF-1 α regulates cells' responses to hypoxia and may be involved in reducing tissue damage and increasing disease tolerance. So, the scientists administered a drug called 1,4-DPCA, which is known to enhance the activity of HIF-1 α via a separate but related mechanism. This drug increased *Xenopus* embryo survival to more than 80% in the presence of deadly bacteria. When the researchers added an inhibitor of HIF-1 α

along with 1,4-DPCA, the embryos succumbed to infection, confirming that HIF-1 α is indeed a key player in infection tolerance.

Crucially, the *Xenopus* genes that underwent the greatest changes in their expression levels due to treatment with 1,4-DPCA were also present in the 20-gene signature of pathogen tolerance that the researchers had identified previously, suggesting that the drug mimics aspects of natural tolerance including modulating [genes](#) involved in metal ion binding.

"Ever since the germ theory of disease began to be accepted by science in the 19th century, treatment has focused on the pathogens themselves. But these experiments show that modulating a host's physiological responses to a pathogen deserves an equal amount of attention, and could offer a sorely needed alternative approach to treating disease," said co-author and Wyss Associate Faculty member Michael Levin, Ph.D., who is also the Vannevar Bush chair and Director of the Allen Discovery Center at Tufts University.

However, the researchers caution that tolerance-inducing drugs are not a silver bullet against infections. Increasing humans' tolerance to infection could mean that they never fully clear a harmful pathogen from their bodies, which could have long-term health effects. In addition, these people with persistent, low-grade infections could spread the pathogen to others who are more susceptible. Therefore, drugs that increase tolerance are likely best used in combination with other measures like vaccines, or in isolated emergency situations such as protecting doctors and nurses who are responding to a deadly pathogen outbreak.

"This is wonderful example of turning scientific or medical paradigms on their heads: rather than searching for yet another highly targeted antibiotic that pathogens will develop resistance to in the future, we chose to discover ways to stimulate the host to be tolerant to a broad

range of infections. While this work is far from the clinic, it demonstrates the value of thinking outside the box, and opens up new approaches to therapeutics development," said senior author and Wyss Founding Director Donald Ingber, who also is the Judah Folkman Professor of Vascular Biology at Harvard Medical School (HMS) and Boston Children's Hospital, and Professor of Bioengineering at the Harvard John A. Paulson School of Engineering and Applied Sciences.

The team is continuing to investigate stress responses similar to those found in pathogen [tolerance](#) in *Xenopus*, now largely in the context of the Wyss Institute's Biostasis project.

Additional authors of the paper include former Wyss Institute members Vishal Keshari, Alexandre Dinis, and Diogo Camacho, Ph.D.; Mark Cartwright, Ph.D., a Senior Scientist at the Wyss Institute; Jean-François Paré Ph.D., from Queen's University, Ontario, Canada; and Michael Super, Ph.D., a Lead Staff Scientist at the Wyss Institute.

More information: Megan M. Sperry et al, Enhancers of Host Immune Tolerance to Bacterial Infection Discovered Using Linked Computational and Experimental Approaches, *Advanced Science* (2022). [DOI: 10.1002/advs.202200222](https://doi.org/10.1002/advs.202200222)

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