that's not an inline six but a V8 engine," he points out, "you're also going to need a bigger catalytic converter."

Interestingly, a 2009 study showed that the widespread practice of antioxidant vitamin supplementation can actually interfere with this natural response. For the experiment, researchers divided human subjects into four groups: exercisers who took antioxidant vitamins; exercisers who did not; non-exercisers who took antioxidant vitamins; and non-exercisers who did not. Both groups of exercisers were healthier after a few months. But surprisingly, those who exercised *without* the antioxidant vitamins did best, probably, Mootha speculates, "because the rest of the cell, when it senses some of these sparks, adapts in a way that is beneficial to the organism"—and does so better than *with* vitamins, which appeared to interfere with the health-promoting stress of physical exercise.

This result didn't surprise him, because of the numerous adaptive responses to stress already known to be mediated through the mitochondria, evolved during a billion-year history. In this long view, any mutations that did not kill an individual cell (or the larger organism) might have opened the way for subsequent mutations that would bypass—or "rescue"—the damaged link in the chain of chemical reactions mitochondria use to make energy. In some cases, in other words, the evolved response of the organelle and host cell to the overloaded or damaged pathway can actually provide a net benefit to both the cell and the entire organism.

An interesting example of this overcompensation, Mootha says, occurs when diabetes patients are given Metformin, which *interferes* with normal mitochondrial function. The drug "has only one known target," he explains: the first stage in the five-step process by which mitochondria produce energy. When that initial step is severely impaired, as in cases of mitochondrial disease, the results are devastating. But the *weak* inhibition caused by Metformin triggers an adaptive response that actually *helps* diabetes patients. "It's a little bit like Mithridates, the Persian king who was afraid of getting poisoned, so he had his pharmacist mix all the poisons available and then took sublethal doses," Mootha points out—and perhaps not all that different from a vaccination. Metformin induces "a state called hormesis, a protective response that's net protective." The effect is so promising that researchers recently began testing Metformin in human clinical trials to see whether hormesis can slow aging. The mechanism has been worked out at the genetic level in worms, but in higher organisms, he continues, "we actually don't know what that program is right now. The mitochondrion is this beautiful organelle, but there are all these homeostatic and feedback loops within it" which are in turn "wired within the broader organism," which has its own loops and feedback mechanisms.

With his computational background, Mootha has the tools and training to tease out the nature of this complexity, and use powerful, scaled approaches to develop new therapies. Inspired by the example of Metformin, he and colleagues initiated a genome-wide screen in 2014, with support from the Marriott Foundation. Searching for factors that, when disrupted, allow cells to cope with broken mitochondria, they got a hit. Their screen suggested that low levels of atmospheric oxygen could trigger a response that protects against Leigh syndrome, an inherited disease of the central nervous system—caused by mutations in any one of 75 different genes—that in children ends in death between the ages of three and 16 months, frequently as a result of respiratory failure.

When the researchers tested the idea in mouse models of mitochondrial disease, the results were astounding. While a normal mouse lives about two years, their diseased mice typically survived for just 55 days. But when the team lowered the oxygen concentration to 11 percent, a level typically found at altitudes of around 14,000 feet, they

From Physiology to Systems Biology

Systems biology shares with physiology, a much older discipline, the desire to study how whole biological systems work and are integrated. In the 1930s, Harvard Medical School (HMS) professor of physiology Walter Cannon coined the term "homeostasis" to describe how the brain and various parts of the body talk to each other to maintain a stable internal equilibrium. "The limitation of that approach in the modern age," explains Marc Kirschner, "is that most of the action is taking place at the molecular level."

Kirschner, who founded the HMS department of systems biology in 2003 and chaired it until this spring, explains that, "whether in genetics, where mutated genes are expressed as proteins, or in pharmacology, where drugs (small molecules) interact with those proteins, the key interactions are at the microscale. Geneticists, cell biologists, and biochemists all work at this scale, but systems biology" is different because, like physiology, the field "aims to understand the *dynamic interactions among* components at that molecular level."

Kirschner hired Mootha as the first faculty member for the new department in 2004. "What made Vamsi attractive," he says, is that his field of study, metabolism, "is an integrated problem. It is not just figuring out what the pathways are, but how metabolism works to meet the constantly changing needs of the organism." Mootha also brought an interdisciplinary approach to his focus on mitochondria, these machine-like systems that "influence, and are in turn influenced by, virtually every other part of the cell."

Kirschner recalls that Mootha first used his background in mathematics to tease out the fingerprints of genetic changes that were important in diabetes. At the time, other researchers were finding genetic associations to diabetes that were not statistically reliable, he continues. Mootha "very cleverly grouped the changes in terms of systems. That increased their statistical significance, because he was looking at lots of associations, not just one thing at a time." Mootha thus demonstrated the important role of mitochondria and oxidative metabolism in diabetes, and that "had a big impact," Kirschner adds. Again and again, Mootha has used a blended approach to systems biology, combining the tools of genomics (he maintains an affiliation with the Broad Institute, where he co-directs the Metabolism Program) with direct measurements of variables such as oxygen uptake or calcium flux—the microphysiology that characterizes a greater proportion of the systems biology research taking place at HMS. Says Kirschner, "Vamsi is an absolute master at matching the approach to the system, and his work developing hypoxia as a treatment for mitochondrial disease is a beautiful example of using genomic tools to get at a physiological problem, with direct medical application."