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The 2015 HHMI Investigators: M-Z

John D. MacMicking, PhD
Yale University

The human body has an army of dedicated immune cells evolved to fight infection. But recent work suggests that skin cells, heart cells, neurons, and even single-celled bacteria – most cells, in fact – have antimicrobial defenses of their own. John MacMicking studies these newly emergent self-defense systems, which have been collectively termed cell-autonomous immunity. His discoveries about how individual cells protect themselves against viruses, bacteria, and other pathogens is forcing scientists to reconsider what constitutes the boundaries and breadth of the traditional immune system. His lab's focus is on how we control and eliminate intracellular microbes once they are recognized by the body's immune sensors. In humans and other mammals, hundreds of genes participate in these elaborate defense systems, switching on the production of antimicrobial proteins in response to either a cell's alarm signals or direct detection of a pathogen. As a graduate student, MacMicking generated some of the first genetic mutants to reveal a role for these cell-intrinsic pathways, including ubiquitous gases such as nitric oxide that are critical for resistance to infection. In his own lab, his team identified a new family of enzymes, called GTPases, expressed in both immune and non-immune cells, that help tailor their defense strategies in accordance with where the pathogen replicates. Some of these GTPases, for example, target microbe-killing proteins to intracellular compartments harboring sequestered pathogens, whereas others direct protective responses within the host cell cytosol or the nucleus. His lab is currently assembling a biogeographical map of these host defense networks to decipher the language of intracellular immunity in higher species such as mammals.

Andreas Martin, PhD
University of California, Berkeley

The proteasome – the molecular machine responsible for disposing of damaged or obsolete proteins – is so crucial to healthy cells that researchers have had a hard time studying it. Anytime scientists tried to manipulate the proteasome inside cells, the cells would die. Andreas Martin spent several

years devising a production system in bacterial cells as well as assembly strategies in the test tube to reconstruct fully functional proteasomes, each of which has at least 34 different subunits, so he could examine their structure and function in detail. Now his work is offering a new framework for understanding how the proteasome is able to specifically degrade hundreds of different proteins in the cell. Martin's lab group used cryo-electron microscopy to reveal the architecture of the proteasome, showing how its subunits fit together and where key components are positioned to interact with proteins tagged for disposal. One of these structures captured the proteasome at work, as a target protein passes the gated entry portal toward the barrel-shaped core of the proteasome. Together with detailed biochemical studies, this structure revealed that the proteasome changes shape when it recognizes a target protein, allowing that protein to enter. The group has also determined the contributions of six energy-harnessing enzymes that are arranged in a ring-shaped structure with a spiral-staircase configuration and that function as the molecular motor to actively pull target proteins into the proteasome's interior. Martin considers what his group has learned thus far a foundation for even more ambitious investigations detailing the steps and regulation involved in proteasomal degradation.

Joshua T. Mendell, MD, PhD
University of Texas Southwestern Medical Center

When Joshua Mendell set up his research lab in 2004, the study of microRNAs was an emerging field. Hundreds of these small bits of RNA had been found in plants and animals, and scientists knew they affected a variety of biological processes by regulating gene activity. Mendell dove in and quickly established himself as a leader in determining how microRNAs influence development and disease. His first big discovery came in 2005, when he showed that a well-known cancer-promoting protein, MYC, directly stimulates production of a specific cluster of six microRNAs. He and others have since demonstrated that these microRNAs contribute to MYC's ability to drive tumor formation. Work from Mendell's team has revealed involvement of microRNAs in several other critical cancer pathways as well, and recently the lab showed that certain microRNAs are important for wound healing. Mendell's group has also uncovered new mechanisms through which the abundance of microRNAs is controlled in normal tissues and in tumors. Ultimately, Mendell is interested in developing new therapies for human disease, and his work in animal models has provided persuasive evidence of the therapeutic potential of microRNAs. His team slowed the growth of liver tumors in mice dramatically by giving the animals a specific microRNA that was present at lower levels in cancer cells than in healthy liver cells. The treatment killed tumor cells but preserved healthy cells, suggesting that such therapies might be well tolerated and effective.

Joseph D. Mougous, PhD
University of Washington

Joseph Mougous says it's a mistake to assume that bacteria operate as independent cells just because they are single-celled organisms. Bacteria intermingle in the environment, and Mougous has uncovered surprisingly sophisticated and diverse ways in which they interact when in close quarters. As a postdoctoral researcher, he studied a secretion system present in hundreds of bacterial species. His own lab has gone on to discover that these microbes usually employ the system to deliver toxic proteins to other bacteria, rather than the predicted target, host cells. Many bacteria use the system against microbial species competing for the same resources. They even inject the toxic proteins into their own kin, but Mougous showed that each species produces immunity proteins that prevent self-harm. By studying these interactions cell by cell, his team has found that the weaponry has a downside: activating the system triggers competitors to respond by activating their own toxin-delivery systems. Mougous's group recently discovered that, throughout evolution, many nonmicrobial species have co-opted genes that encode these bacteria-killing toxins. They found one such gene in deer ticks, and have shown that the encoded protein inhibits proliferation of the bacterium that causes Lyme disease.

Kim Orth, PhD
University of Texas Southwestern Medical Center

Bacteria will do whatever it takes to outwit their hosts. Kim Orth's lab studies their crafty ways, figuring out exactly how pathogens manipulate host cells for their own benefit and survival. Her team's work has uncovered unexpected strategies that bacteria use to survive and spread. Her research group has also helped discern normal signaling processes in host cells, including mechanisms that can be exploited to treat disease. They have found that *Yersinia*, the bacteria that causes plague, silences cells' attempts to summon immune cells by chemically modifying a key signaling protein so that it can no longer be switched on. Their studies of *Vibrio parahaemolyticus*, a bacterium that causes food-borne illness, showed that the microbe injects a toxin into host cells that remodels the cell's structure, causing it to engulf the bacteria. Once inside, bacteria grow and divide until the host cell ruptures. Studies of another *Vibrio* toxin by Orth and her colleagues revealed a previously unrecognized way in which cells chemically modify their proteins to alter their function. The bacteria use the modification, which Orth named AMPylation, to cause host cells to collapse and die. Her team has also discovered a protein that many bacteria use to adhere to cells during the early stages of infection, and is testing whether they can interfere with that attachment to prevent or weaken infections in patients.

Jared Rutter, PhD
University of Utah

Jared Rutter is drawn to biology's least explored areas. His penchant for confronting the unknown has paid off: since launching his research program in 2003, Rutter has turned up answers to mysteries scientists have been trying to solve for decades. His lab group is focused on better understanding mitochondria, organelles that are key to cellular metabolism, signaling, and cell death, and whose dysfunction has been implicated in a variety of diseases. Yet surprisingly, hundreds of known mitochondrial proteins remain uncharacterized. Rutter and his team have identified 30 unstudied families of mitochondrial proteins found in almost all organisms and have begun teasing out their functions one by one. This strategy led to the identification of a long-sought protein complex that transports pyruvate molecules into mitochondria, an important step in the conversion of carbohydrates into usable energy. The discovery has enabled Rutter and other scientists to explore the transporter's role in cancer and other diseases. His team has similarly identified the function of a number of other mitochondrial protein families, empowering the scientific community to explore a range of questions about physiology and disease – and Rutter says that's just the beginning.

Pardis C. Sabeti, DPhil, MD
Harvard University

Computational geneticist Pardis Sabeti uses the evolutionary record embedded in the human genome to guide her to a new understanding of disease. Her lab's computational methods for detecting recently evolved traits have uncovered genetic adaptations that altered humans' malaria resistance, hair and sweat development, and immune responses to bacteria. When her analyses led her to a human gene associated with increased risk of infection by Lassa virus, a devastating pathogen that kills thousands each year in West Africa, she and her colleagues developed a research program for biosafety level-4 (BL-4) viruses in rural parts of Nigeria and Sierra Leone to study the virus and its role in human evolution. In the weeks following the 2014 outbreak of Ebola, Sabeti's team used the tools it had developed for studying BL-4 viruses to rapidly sequence and analyze 99 viral genomes from infected patients in Sierra Leone. These data, which confirmed that the virus was spreading between humans, also revealed how the virus was mutating. The team's results informed strategies for diagnosing the disease and curbing its spread. Sabeti's research team continues to examine the genomes of humans and deadly viruses for clues to how each has influenced the other's evolution. Her approach could transform future response to infectious disease outbreaks.

Jay Shendure, MD, PhD
University of Washington

Science is experiencing a genomics revolution, and Jay Shendure is one of the innovators sustaining its momentum. His work has helped make DNA sequencing faster, cheaper, and more informative. Shendure is a methods developer at heart, but his deep knowledge of medicine and genetics keeps him focused on new technologies that can make a big impact on our understanding of biology and disease. As a graduate student, Shendure laid the groundwork for today's next-generation sequencing when he developed a method for genome sequencing that simultaneously analyzes millions of DNA molecules – an approach only about one-tenth as expensive as conventional methods. In his own lab, Shendure developed a platform for sequencing only the genome's protein-coding regions – the exome – and demonstrated how this cost-effective strategy can identify disease-related gene mutations. Labs around the world have since used exome sequencing to discover genes associated with hundreds of human disorders. More recently, Shendure's team showed that it's possible to sequence the complete genome of a fetus from samples obtained noninvasively from the parents. As Shendure and others apply his methods to real problems, his cross-disciplinary lab team continues to develop new technologies.

Krishna V. Shenoy, PhD
Stanford University

Krishna Shenoy brings an engineer's perspective to his research on how the brain guides body movements. That perspective has led him to unique insights into the dynamic neural circuits that control motor activity. It also keeps his research team focused on gaining knowledge and developing technologies aimed at restoring movement for people with paralysis. By studying the brains of primates as they execute specific tasks, Shenoy and his colleagues have probed how groups of neurons coordinate and cooperate with one another to generate arm movements. Their computational analyses of large-scale neural data show how populations of neurons involved in motor activity evolve dynamically, prompting neuroscientists to reconsider how neural circuits function. As Shenoy and his group investigate the basic principles the brain uses to control movement, they are applying what they learn to the development of medical technologies. Shenoy is also considered a leader in the emerging field of brain-machine interfaces to control the movement of computer cursors and prosthetic limbs. He has developed computational methods to dramatically speed up computers' ability to decode messages from a person's brain. These algorithms have been incorporated into a system designed to allow people with paralysis to control a computer cursor with their thoughts; this system is being evaluated in a clinical trial.

J. Paul Taylor, MD, PhD
St. Jude Children's Research Hospital

Paul Taylor trained as a clinical neurologist. He now spends his days in a research lab investigating how the nervous system develops and functions, but his studies always begin with what he learns from patients. Beginning with genes that are disrupted in patients with neurodegenerative diseases, Taylor's lab team first determines the normal function of those genes and then looks at how their mutation causes disease, taking advantage of any model or experimental system that gets the researchers closer to an answer. This strategy has led Taylor to discover that some neurodegenerative diseases, including amyotrophic lateral sclerosis and frontotemporal dementia, are caused by defects in the assembly, disassembly, or clearance of cellular packages of RNA and protein known as RNA granules. He has shown that these types of defects in RNA metabolism can also cause degenerative muscle diseases. Taylor's team is now investigating the role of RNA granules in regulating gene activity and exploring how the granules are assembled.

Doris Y. Tsao
California Institute of Technology

When Doris Tsao first coaxed monkeys into an functional MRI (fMRI) scanner to watch their brains respond to images of faces, she saw blood flow increase in several regions of the brain. She and her colleagues used the blurry blobs of neural activity indicated by the fMRI scan to guide more precise studies. To the team's surprise, those experiments revealed that there were six distinct regions of the brain dedicated to processing information about faces. Tsao called these face patches. Over the last decade, her lab has learned that these face patches work together to recognize and discriminate between faces, and revealed computational strategies the cells use to accomplish this task. Her team has identified neurons that respond specifically to certain facial features, such as hair thickness or iris size, and found cells that respond selectively to the faces of only a few individuals. Her group's work on the primate face-processing system is part of her larger goal of understanding how the brain represents objects. Tsao is now planning new research to examine the neural circuitry that integrates discrete visual features into the perception of whole objects.

Tobias C. Walther, PhD
Harvard University

When the little balls of fat that float in our cells grow and accumulate excessively, they can cause a variety of health problems, including obesity, diabetes, and heart disease. But these lipid droplets play a vital role in cells: storing energy as well as the materials needed to build and maintain biological membranes. Tobias Walther wants to understand the molecular mechanisms behind lipid storage in cells. With colleague Robert Farese, he identified more than 200 genes that regulate lipid storage. He discovered that there are two

classes of lipid droplets: small, static droplets and larger droplets that expand as needed. Walther showed how enzymes involved in synthesis of triglycerides (one type of lipid stored in the droplets) locate and engage with the expanding droplets to build new triglycerides. His team also studies how membrane lipids not stored in droplets are kept in balance inside cells. Ultimately, Walther aims to uncover the biochemical and physical principles that govern lipid balance and storage and to determine how alterations in lipid stores affect physiology and disease.

Joanna K. Wysocka, PhD
Stanford University

Joanna Wysocka wants to understand the gene expression controls that operate during development to make human faces distinct from other animals, and that make each face unique. To decode the genetic instructions that orchestrate the transformation of a single-celled zygote into a complex organism, Wysocka and her team are focusing on neural crest cells. As these cells migrate through a developing embryo, they take on specialized identities and become parts of various body systems, including the skeletal and connective tissue of the head. Wysocka's team has discovered thousands of sequences in the human genome that likely control expression of specific genes in neural crest cells. Her team studies how variations in these sequences may result in differences in human face shape, or lead to birth defects such as cleft palate. She is also interested in understanding how changes in regulatory DNA elements gave rise to morphological changes during evolution that made human faces distinct from those of other great apes. In addition to providing insights into craniofacial development and disease, Wysocka's work is uncovering broad principles about gene regulation, including the existence of chemical signatures on DNA-packing proteins that can guide researchers to regulatory elements that might otherwise remain hidden in the genome.

Jennifer A. Zallen, PhD
Memorial Sloan-Kettering Cancer Center

As an embryo grows and transforms, its cells divide, shift, and take on new identities. Jennifer Zallen is studying the coordinated cell movements that shape the emerging animal form. She studies how large populations of young cells reorganize to become the elongated beginnings of a body, a transition that requires hundreds of cells to align their movements along a common axis. Working on the fruit fly, her research team discovered that cells at this early stage form pinwheel-shaped rosettes, in which groups of cells line up and then rapidly reorganize themselves to create distance between the fly's future head and tail. This process involves coordinated contractile structures that extend across multiple cells, contracting and pulling the cluster into a rosette. This

rosette mechanism has now been shown to be a fundamental strategy for tissue elongation that is conserved from flies to mammals. In addition, Zallen's team has identified a molecular code that systematically orients cell movements throughout the embryo and orchestrates this dramatic shape change. This work, unraveling the molecular signals and biophysical forces that shape developing embryos, is an important foundation for understanding how errors in these processes lead to birth defects, kidney disease, and cancer.
