Foreign minds, fenceless imagination: The 2013 Vilcek Foundation Prizes

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Ideas to make your hair stand up, just as if you were to stick your finger in a socket.

—Charles Simic (American poet, born in Serbia)

Every year, the White House announces the winners of the National Medal of Science and the National Medal of Technology and Innovation. Awarded during a special ceremony by the president, these medals represent the highest honors bestowed by the United States government on scientists and engineers. In his address during the White House awards ceremony in the fall of 2011, President Obama noted that nine of the 12 honorees were born outside of the U.S. (1). The winners came to the U.S., he said, because "America is the best place in the world to do the work they do."

At a time when immigration counts as an issue of pressing political currency, the importance of foreign-born scientists to the U.S. biomedical research enterprise bears repeating: the proportion of foreign-born researchers among recipients of high honors bestowed on American scientists typically exceeds the percentage of foreign-born people living in the U.S., which—including undocumented aliens—hovers around 13% of the general population (2). In fact, at least one in three scientists honored with the Nobel Prize in Physiology or Medicine for work done in the U.S. during the past century was born outside of the country (3).

The United States is a nation of immigrants, and most Americans are proud of their ancestral roots. Nevertheless, a significant portion of the populace subscribes to the view that new immigrants are a burden on the country's economy. To raise public awareness of the invaluable contribution of immigrants to science in America, the Vilcek Foundation initiated an annual program of prizes to recognize accomplished foreign-born biomedical scientists who are widely regarded as leaders in their fields (**Table 1**). Currently, each of these prizes includes a cash award of $100,000 (3–5). To recognize a younger generation of distinguished immigrant scientists, the Vilcek Foundation established annual Prizes for Creative Promise in 2009; to be eligible, applicants must be 38 years of age or younger (4–5). In 2013, three winners of the Prize for Creative Promise in Biomedical Science were selected, and each winner was awarded a cash prize of $35,000 (**Table 2**). Similarly, the Vilcek Foundation (5) confers annual prizes on prominent, foreign-born artists for outstanding achievement in various artistic endeavors. This year, the Vilcek Prize in Biomedical Science is shared by immunologists Richard Flavell and Ruslan Medzhitov, both Howard Hughes Medical Institute Investigators in the Department of Immunobiology at Yale University.

From a quiet English town, a jewel in Yale's crown: Richard Flavell, co-recipient of the 2013 Vilcek Prize for Biomedical Science

For decades, the laboratory mouse has been held up as a microcosm of human biology, a model that lends itself to scientific explorations of disease and tests of vaccines and drugs. Yet, despite the genetic similarities between mice and humans that make such pursuits meaningful, experimental drugs that appear effective in mice often fail when tested in people, leading to a growing need for mouse models that better represent human physiology. Yale University immunologist Richard Flavell, co-recipient of the 2013 Vilcek Prize for Biomedical Science, has used years of immunological insights to create just such a model. Just as he has assembled a trove of findings on human immunity into a towering intellectual edifice, Flavell hopes to build, gene by engineered gene, a mouse model with a working human immune system. Such a model could help researchers fashion vaccines and drugs that have a fighting chance in the human body (**Fig. 1**).

As a teenager growing up during the late 1950s in Wimborne, a once-monastic town that sits at the confluence of rivers in Southwest England's Dorset county, Flavell was largely uncharmed by science. By the turn of the decade, social change swept through Britain, marking the era with all manner of cultural movements. Smitten with rock-and-roll, blues, and American pop music, Flavell banded together with friends to play music at local events. But a high school chemistry course piqued his curiosity and proved to be a turning point in his trajectory. "That was an infectious process, so that made me interested in many more things," he says, remembering a time when he traded youth's

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Richard Flavell. Photo credit Yale University.

callowness for intellectual voracity. Before long, a deep-seated awe of nature combined with a newfound appreciation for chemistry nudged him toward an undergraduate degree in biochemistry at the University of Hull in Yorkshire.

At Hull, Flavell learned to biochemically characterize enzymes, focusing on a pair of closely related enzymes involved in energy generation in mammalian cells. The experience whetted his appetite for biological research, leading him toward doctoral studies at Hull. "It was a new biochemistry department and had a tremendous *esprit de corps*," recalls Flavell. In 1967, in the wake of the discovery that mitochondria, the microscopic powerhouses that sustain cells, carry their own complement of genetic material, Flavell applied himself to unraveling the physical properties of the mitochondrial genome in a protozoan called *Tetrahymena,* a molecular biology workhorse. The findings, which helped settle an unresolved question on the mitochondrial DNA's configuration, were published in a 1970 issue of the *Biochemical Journal* (7).

Having earned his doctoral degree, Flavell went to the Netherlands for an apprenticeship with Dutch molecular biologist Piet Borst at the University of Amsterdam, where he continued to study mitochondrial DNA, thanks to a fellowship from Britain's Royal Society. "I realized it was important to work with great scientists. Great scientists learn from other great scientists," he says. True to the aphorism, Flavell pursued another postdoctoral stint, this time with molecular biologist Charles Weissmann at the University of Zurich in Switzerland, upon the recommendation of Borst.

Despite his sprawling work in immunology, Flavell is perhaps best known among biologists for a game-changing contribution to genetics that was shaped by his work in Weissmann's lab. During the early 1970s, when recombinant DNA technology was a fledgling enterprise, researchers uncovered the actions of genes largely by studying their effects. Clues to the genetic underpinnings of traits came from analyses of the traits themselves, following a traditional experimental tack called forward genetics. Flavell and Weissman upended the logic of the approach, intentionally inducing mutations in genes to study their effects on observable traits. Thus was born what later became the molecular biologist's time-honored tool: reverse genetics. "There were whole components of genomes for which we had no obvious function. So we decided to mutate the genome and determine the consequences of selected mutations," says Flavell. Describing how to manipulate with pin-sharp precision the genome of a virus that infects bacteria, Flavell and Weissmann committed to print the concept of "site-directed mutagenesis"—a lapel-grabbing advance in the mid-1970s that has now earned a permanent place in the molecular biology lexicon—in a 1974 report in the *Journal of Molecular Biology* (8).

Reverse genetics, which has since become *de rigueur* in analyzing the functions of genes, helped cement Flavell's reputation and earned him a faculty position at the University of Amsterdam, where he returned in 1974 upon the wishes of his Dutch girlfriend and the urging of his mentor Borst, who, by then, was convinced of his protégé's scientific ingenuity and pedagogical earnestness. "Also, Amsterdam had a wonderful air of democracy, which was very different from Britain, which was still a bit stuffy because of the class system," says Flavell, recalling his penchant for scientific free-thinking that brought him back to the Netherlands.

During his second stint in Amsterdam, Flavell pledged himself to the practice of reverse genetics but with an ambitious goal: cloning a mammalian gene at a time in history when a molecular notion of genes in mammals was, at best, nebulous. Moreover, cloning was a parlous enterprise, partly because vehement opposition to recombinant DNA technology in the Netherlands over concerns about the method's safety posed impediments to progress. (Two years earlier, the now-famous Asilomar Conference on recombinant DNA had issued a moratorium on most mammalian gene cloning.)

Unwilling to shelve a project into which he had made substantial inroads, Flavell partnered with Weissmann in Zurich to clone a gene from rabbit blood cells, proving that it was possible to visualize individual genes in mammalian DNA. Soon thereafter, Flavell and his then-postdoctoral fellow Alec Jeffreys found that mammalian genes contain runs of nucleotides—now called introns—that interrupt their protein-coding sequences (9). Now known to play pivotal roles in gene regulation, introns were the subject of the 1993 Nobel Prize in Physiology or Medicine, shared by molecular biologists

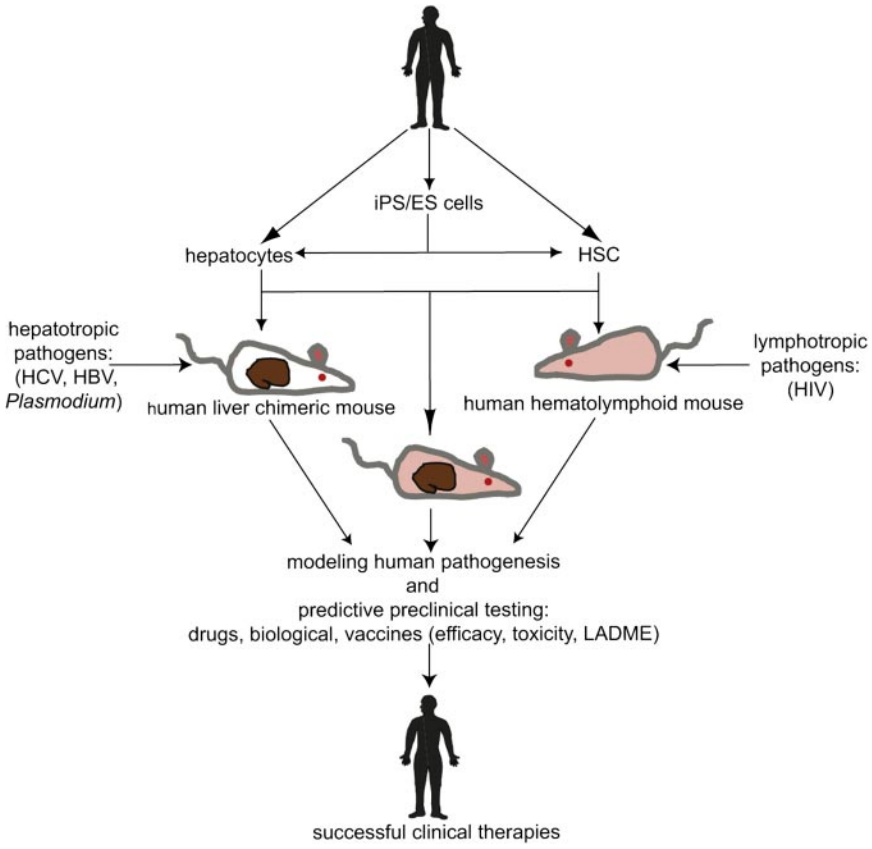

Figure 1. Humanized mice help researchers study infectious diseases. iPS, Induced pluripotent stem cells; ES, embryonic stem cells; HSC, hematopoietic stem cells; LADME, liberation, absorption, distribution, metabolism, excretion. Reprinted from ref. (6), with permission from Elsevier.

Philip Sharp and Richard Roberts, who had discovered split genes in viruses a few months before Flavell and Jeffreys published their findings on the rabbit gene. "Our mammalian work showed that the phenomenon was neither unique to infectious viruses nor limited to noncoding gene segments," says Flavell. Before long, Flavell and his coworkers found that the activity of the rabbit gene's human counterpart is controlled by a chemical modification called methylation (10, 11).

After stints at London's National Institute for Medical Research and at the Massachusetts-based biotech firm Biogen, Flavell struck roots at Yale University, where he was lured in 1988 to launch an immunology research program as a Howard Hughes Medical Institute investigator. At Yale, Flavell brought his expertise in reverse genetics to bear on an array of questions in immunology.

Among those forays, Flavell focused on a challenge whose origin can be traced to his adopted home. More than a decade before he arrived at Yale, a pair of researchers there had discovered Lyme disease—a potentially debilitating illness caused by a bacterium and spread by the bite of blacklegged ticks—in the Connecticut town of Lyme, which lent the disease its name. Together with a young physician-trainee, Erol Fikrig, now chief of Yale's infectious diseases section, Flavell fashioned a vaccine that prodded the immune system of mice to produce antibodies against a protein on the surface of Lyme bacteria, keeping the bacteria in check and the disease at bay. "At the time, many people said, 'You can't make a vaccine against Lyme disease because you don't get good immune responses during infection'," recalls Flavell. But the findings, published in *Science* in 1990 (12), belied that view, deftly laying the foundation for the development of a human Lyme disease vaccine. Two years later, Flavell's team reported in the *Proceedings of the National Academy of Sciences USA* (13) that the vaccine could eliminate the bacteria from ticks that fed on the blood of vaccinated mice, raising hope for a vaccine against human infections acquired through tick bites.

Before the turn of the decade, the U.S. Food and Drug Administration approved LYMErix, a vaccine against Lyme disease, developed through a partnership between Flavell's team and SmithKline Beecham Pharmaceuticals, for use in 15- to 70-year-old people. But controversy surrounding the often-contested symptoms of Lyme disease scuttled the success of the vaccine, whose manufacture was later discontinued. Today, Lyme disease is treated by long courses of antibiotics; no approved human vaccine exists, according to the Centers for Disease Control and Prevention. In 2002, Flavell and others found that people who mounted poor immune responses to the vaccine in Phase III clinical trials harbored lower-than-normal levels of a protein called TLR1, which acts a molecular handhold for Lyme bacteria, on the surfaces of immune cells called macrophages, which help fight infections (14). The findings partly explained the vaccine's poor performance in some elderly people.

Since 2005, Flavell has devoted much of his intellectual capital toward a global health challenge laid down

TABLE 1. *Recipients of the Vilcek Prizes in biomedical science 2006–2013*

Year	The Vilcek Prize			The Vilcek Prize for Creative Promise[a,b]		
	Name	Country of birth	Institution	Name	Country of birth	Institution
2006	Joan Massagué	Spain	Memorial Sloan-Kettering Cancer Center	None		
2007	Rudolf Jaenisch	Germany	Massachusetts Institute of Technology	None		
2008	Inder Verma	India	Salk Institute	None		
2009	Huda Zoghbi	Lebanon	Baylor College of Medicine	Howard Chang	Taiwan	Stanford University
2010	Alexander Varshavsky	Russia	California Institute of Technology	Harmit Malik	India	Fred Hutchinson Cancer Research Center
2011	Titia de Lange	Netherlands	Rockefeller University	Yibin Kang	China	Princeton University
2012	Carlos Bustamante	Peru	University of California, Berkeley	Alice Ting	Taiwan	Massachusetts Institute of Technology
2013	Richard A. Flavell and	United Kingdom	Yale University School of Medicine	Hashim Al-Hashimi	Lebanon	University of Michigan
	Ruslan Medzhitov (shared award)	Uzbekistan	Yale University School of Medicine	Michael Rape	Germany	University of California, Berkeley
				Joanna Wysocka	Poland	Stanford University School of Medicine

[a]Candidates must not be older than 38 years at the time of selection. [b]As of 2013, the number of Creative Promise Prizes has been increased to three/year.

by the Bill and Melinda Gates Foundation to help create vaccines for diseases plaguing the developing world. To that end, his group has made impressive gains in creating genetically engineered mice that carry a handful of human immune system genes instead of their mouse counterparts. The hope is that such mice will better support the function of engrafted human immune cells, allowing researchers to test the safety and efficacy of experimental vaccines before they are used in human trials. Thanks to a $17 million award from the Gates Foundation, Flavell and his research partners, Sean Stevens at the Tarrytown, NY-based Regeneron Pharmaceuticals and Markus Manz at the Institute for Research in Biomedicine in Bellinzona, Switzerland, have inched toward a model mouse, replacing piecemeal an array of mouse genes, including those that encode proteins that attract immune cells, proteins that lend immune cells their identities, and immune molecules that serve as handholds for viruses and bacteria (15, 16). "The mice that we are now working with have a total of 12 or more modified genes. They can now be used to study typhoid fever, HIV, tuberculosis, cancer and autoimmune diseases like diabetes," Flavell says.

Autoimmune diseases have long captivated Flavell's imagination. Researchers have known that the immune system deploys proteins that recognize the beneficial microbial denizens of the human body. These proteins help maintain harmony between the human immunological armament and microbial endowment, ensuring that helpful microbes don't turn against their hosts. Flavell surmised that a group of immune proteins called inflammasomes, which help mediate inflammation, might be involved in diseases triggered by a bacterial imbalance in the human intestine. Having discovered that disabling specific inflammasomes can trigger a form of inflammatory bowel disease in mice, Flavell tested whether the disease was caused by a defect in the immune cells or by the gut bacteria. "When you mutate a specific inflammasome, the bacterial mix in the intestine changes from a population of bacteria in equilibrium to a population that can trigger pathological changes," he says. And in 2011 Flavell's team found that healthy mice could develop IBD merely by sharing a cage with mice with an altered mix of intestinal microbes, suggesting that an altered gut microbial environment might have a curiously contagious character (17). Extending those findings, his team demonstrated that metabolic syndrome—a composite condition marked by obesity, fatty liver disease, and Type 2 diabetes—could be similarly transmitted among mice by changes in gut microbes and close physical contact (18). "The implications are that we may have to consider a three-pronged approach—antimicrobial, antiinflammatory and met-

abolic—in dealing with some of these diseases, which affect millions of people worldwide," says Flavell.

Firmly embedded in the canon of modern immunology, Flavell's wide-ranging contributions have earned him a wealth of accolades, notable among which are memberships in Britain's Royal Society, the European Molecular Biology Organization, the U.S. National Academy of Sciences, and the Institute of Medicine. Though the path to his ultimate goal—the model mouse—is fraught with challenges, Flavell says he is prepared for the long haul.

From the ruins of empire, a rise to prominence: Ruslan Medzhitov, co-recipient of the 2013 Vilcek Prize for Biomedical Science

If there is a single fact that stands out in the career-defining commonality between Flavell and the co-recipient of the 2013 Vilcek Prize for Biomedical Science, Yale University immunologist Ruslan Medzhitov, it might be that they are both rated among the world's best in their chosen pursuits by more than a few serious scientists. For unraveling the byzantine links between innate immunity—an ancient system of immune sentinels shared by most living beings—and adaptive immunity—a sophisticated cellular armament found only in vertebrates—Medzhitov has earned a richly merited scientific reputation.

The story of Medzhitov's rise to prominence is a triumphal narrative of surmounted hardships and a poignant reminder of the power of ambition. Born in the mid-1960s to mathematicians in the Uzbek Soviet

Ruslan Medzhitov. Photo credit Michael Marshland/Yale University.

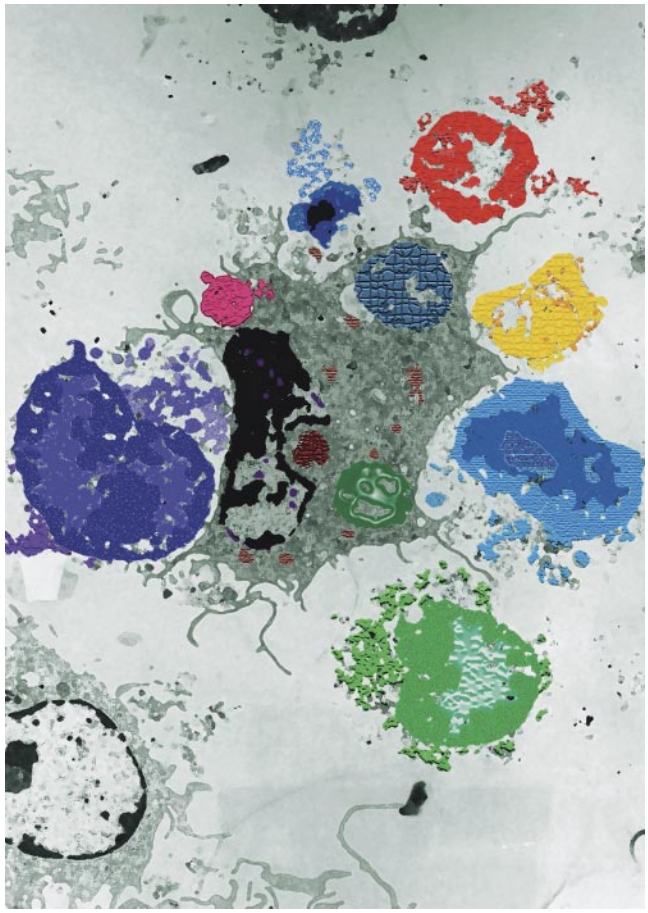

Figure 2. Immune sentinel. False-colored electron micrograph of a mouse macrophage ingesting dead lymphocytes (multicolored) in a laboratory experiment. Image courtesy Julie Magarian Blander.

Socialist Republic, now Uzbekistan, Medzhitov says his fascination with biology was partly driven by a hobbyist's passion for insect collection and a disinclination to follow in his parents' path. He recalls his boyhood wonderment when he learned from his brother that a genetic program controlled the warp and weft of spiders' webs. "At that moment, I decided I wanted to be a biologist; it was a tipping point," he says.

But the road ahead was rife with difficulties; a year after he enrolled at Tashkent University to study biology, Medzhitov was conscripted by the Soviet Army, where he spent two years before returning to college in 1986. But military training, he soon realized, had reduced his mind to a near-blank slate. "I had to return to middle school textbooks to get up to speed to resume college. That was the degree of degeneration I experienced in the Russian military," he recalls.

When he enrolled in 1990 for doctoral studies at Moscow State University with biochemist Vladimir Skulachev, however, the country's political climate disfavored research. As the Soviet empire fell, plunging the economy into a punishing recession, science suffered a serious blow. "All of a sudden, things you

TABLE 2. *Recipients of the 2013 Vilcek Prizes for creative promise in biomedical science*

Name	Country of birth	Title and institution	Research summary
Hashim Al-Hashimi 	Lebanon	Professor, University of Michigan	Dr. Al-Hashimi develops methods that combine NMR and computational approaches to visualize the dynamics of cellular molecules and processes, such as DNA replication, at atomic resolution. He also characterizes RNA molecules, including HIV RNA, in hopes of identifying small molecules with potential anti-HIV activity.
Michael Rape 	Germany	Associate Professor, University of California, Berkeley	Dr. Rape investigates how a small protein molecule, termed ubiquitin, is attached to cellular proteins and how this process of "ubiquitylation" controls cell proliferation and differentiation. He also studies how drug intervention could activate or inhibit ubiquitylation, hoping to uncover new pathways to chemotherapy.
Joanna Wysocka  Photo credit: Christopher Vaughan.	Poland	Associate Professor, Stanford University School of Medicine	Dr. Wysocka's research focuses on epigenetic mechanisms that regulate self-renewal and differentiation. Concerned with the molecular basis of developmental plasticity, her work centers on two cell types: embryonic stem cells and neural crest cells. She studies how instructions encoded by the genome are interpreted in the context of a cellular state and signaling milieu to establish chromatin states permissive or restrictive for gene expression.

took for granted—like food—became scarce," he remembers. "At one point, my stipend was not enough even for a monthly bus pass to get to work."

Yet, the straitened circumstances failed to dampen his scientific enthusiasm. Unable to find support for experimental research during the economic slump, Medzhitov read voraciously on an array of topics, from molecular evolution to the workings of the immune system, struggling to gain access to scientific literature.

While perusing a hard-won copy of the 1989 proceedings of the *Cold Spring Harbor Symposia on Quantitative Biology* at the Academy of Natural Sciences library in Moscow, Medzhitov was struck by an introduction written by the late Yale immunologist Charles Janeway. Peppered with thought-provoking aperçus, the report laid down a theory on how the innate immune system recognizes patterns on the surfaces of invading pathogens and signals to the adaptive immune system that trouble is afoot, thus helping to mobilize troops against the foes (19). Medzhitov wasted no time writing to Janeway, engaging the well-known immunologist in a scientific exchange that showcased his own intellectual promise. Janeway was suitably impressed—so much so that he offered Medzhitov a postdoctoral position in his lab at Yale, where Medzhitov went in 1993 after graduating from Moscow. While a student at Moscow, Medzhitov had spent a 3-month-long UNESCO sponsored sojourn in the laboratory of the University of California San Diego biochemist Russell Doolittle, who taught him the essentials of computational biology. There, he met immunologist Richard Dutton, whose recommendation later proved pivotal to his postdoctoral position with Janeway.

The elegant simplicity of Janeway's theory of immunity, as yet unproven by experiment, appealed to Medzhitov's aesthetic sensibility, and he set about putting the theory to the test. "We wanted to find a specific gene that would support the theory and explain the connection between innate and adaptive immunity," says Medzhitov. For all its logical appeal, the theory took years to prove, but when Medzhitov and Janeway announced in a 1997 *Nature* report (20) that they had found a human lookalike of a fruit fly protein called Toll receptor, which triggered an adaptive immune response upon infection, they added to the growing interest in a once-tranquil byway of biology. A year earlier, immunologists Bruno Lemaitre, Jules Hoffmann, and others (21) at Strasbourg's *L'Institut de Biologie Moléculaire et Cellulaire* had found that the Toll receptor, known to shepherd embryonic development, moonlights as an innate immune receptor in fruit flies. And when University of Texas Southwestern Medical Center immunologist Bruce Beutler and his team announced in 1998 that a protein called TLR4 helps

immune cells of mice respond to a bacterial product called lipopolysaccharide, which can trigger septic shock, insect and mammalian innate immunity was shown to be of a piece (22). The findings earned Hoffmann and Beutler a share in the 2011 Nobel Prize in Physiology or Medicine. Today, the human TLRs are known to help recognize pathogens through chemical signatures and alert adaptive immune cells to their presence in the body (**Fig. 2**).

Medzhitov's work on the TLRs solidified his position in the field, and when it came time to choose among faculty positions at a handful of top universities, he accepted an offer of assistant professorship from Janeway and Flavell. Medzhitov's partnership with Flavell has resulted in a handful of cowritten reports on TLRs published in journals that rate among the world's most highly cited scientific periodicals. Over the years at Yale, Medzhitov has unearthed a wealth of immunological insights, including the immune system's ability to distinguish between beneficial and harmful microbes. For example, his team found that the microbial signatures that TLRs recognize are often shared by both kinds of microbes, presenting a seeming identity conundrum for the immune system. Contrary to a belief that beneficial bacteria are shielded from immune attack through sequestration in epithelial cells lining the gut, Medzhitov's team demonstrated that the recognition of beneficial bacteria by TLRs helps maintain equilibrium in the mammalian gut, keeping inflammation in check and gut injury at bay (23).

Another example of the labyrinthine immunological mechanisms that Medzhitov brought to light is an inappropriate antiviral immune response triggered in people with a potentially lethal brain disorder called Aicardi-Goutieres syndrome and an often-chronic autoimmune disease called chilblain lupus. This immune response, triggered by so-called endogenous retroviruses, which are permanently embedded in the human genome, is normally kept in check by a mammalian gene called Trex1, thus ensuring that the attack is reserved for viral infections. But Medzhitov and his postdoctoral fellow Daniel Stetson found that in people with the disorders, mutations in the Trex1 gene lead to haywire autoimmune reactions even in the absence of viral infections, thus uncovering a potential drug target for the disorders (24).

For the vast store of intellectual firepower that he brought to bear on basic immunology, Medzhitov has earned many laurels, not least of which are a National Institutes of Health merit award, a Blavatnik Award for young scientists, a Lewis S. Rosenstiel award, the Shaw Prize in Life Science and Medicine, and membership in the U.S. National Academy of Sciences.

Despite the brassy limelight bestowed on him over the years, Medzhitov says formidable challenges loom in his future, including the study of allergy and inflammation.

In addition to Richard Flavell and Ruslan Medzhitov, winners of the Vilcek Prize for Biomedical Science, three young scientists, Hashim Al-Hashimi, Michael Rape, and Joanna Wysocka, were selected from more than 100 applicants as winners of the 2013 Vilcek Prizes for Creative Promise for Biomedical Science. Their accomplishments are summarized in Table 2. FJ

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