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Journey to the Summits of Science: The 2014 Vilcek Foundation Prizes

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I listened to the trees.
They had a secret
Which they were about to
Make known to me,
And then didn’t.
—Charles Simic (American poet, born in Serbia)

EIGHT YEARS AGO, the Vilcek Foundation initiated a program of prizes for foreign-born biomedical scientists who have made major contributions to their fields, while living and working in the United States (1). The purpose of the prizes, which include a cash award of $100,000, is to draw attention to the enormous contribution of immigrant scientists to this country and to celebrate individuals hailing from distant shores without whose hard work the United States would not be the best place in the world for scientific work (2–4). The individuals chosen to receive the Vilcek Prizes by distinguished juries of peers are widely regarded as international leaders in the life sciences (3).

The Vilcek prizes recognize scientists at the pinnacle of their careers. To draw attention to the important role played by a younger generation of foreign-born scientists, the Vilcek Foundation established in 2009 Prizes for Creative Promise in Biomedical Science, open to applicants 38 years of age or younger. Since 2013, three Creative Promise Prizes, each including a cash award of $35,000, are being awarded annually.

The Vilcek Foundation prizes are unique, partly because they are awarded to biomedical scientists born outside the United States. Another unique feature of the prizes is the companion Vilcek prizes, given to foreign-born artists living and working in the United States (5). The relationship between the sciences and the arts can be traced back to the dim mists of history, the results of the cross-fertilization resonant in cultural figures of the Renaissance. Yet few accolades jointly recognize the creativity and originality of scientists and artists.

The 2014 Vilcek Prize in Biomedical Science honors, for the first time in the prize’s history, a prominent neuroscientist. The three recipients of the Vilcek Prizes for Creative Promise in Biomedical Science represent the fields of molecular genetics, neuroscience, and computational biology.

The cartographer of movement: Thomas Jessell, winner of the 2014 Vilcek Prize

Gaining the floor before an audience of peers gathered to celebrate his selection for the Scolnick Prize in Neuroscience at Massachusetts Institute of Technology, Thomas Jessell wryly observed, “If you leave this lecture theater with no other change in your thought, it’s to try and convince you that the spinal cord is not actually a simple system. . . We don’t understand it, and maybe we’ll never understand it.”

Set against his impressive body of work spanning nearly four decades, Jessell’s remark might be more aptly mined for modesty than literal meaning. Beginning with panoramic views on spinal cord development in growing embryos, Jessell, a neuroscientist at Columbia University and winner of the 2014 Vilcek Prize in Biomedical Science, has identified the mo-
lecular signals that shape the fates of embryonic cells destined to become certain types of neurons, mapping, along the way, genes that control the formation of neuronal circuits underlying movement. Through the sustained density and sweep of such efforts, Jessell has tried to disentangle the spinal cord’s workings, unraveling and manipulating the mechanisms that motor the mundane movements of animals as they maneuver the material world.

Academic renown is no stranger to Jessell’s family, which provided ample grist for creative inspiration during his 1960s London childhood: His German-born grandfather was a celebrated organic chemist, whose forays into chemical synthesis led to faculty appointments across the far reaches of Europe, from Oxford to Istanbul; his mother gained transcontinental acclaim as a paintings conservator, whose talent earned her coveted stints at London’s National Gallery, Washington, DC’s National Gallery of Art, and the Getty Museum in Los Angeles.

Given his family background, Jessell’s entry into the academic world may seem a foregone conclusion, yet his decision to pursue science in college was the result of considered choice and subtle influences. Graduating from a private high school in North London in the 1960s, Jessell weighed the merits and demerits of art history and science, eventually favoring pharmacology, which he studied at Chelsea College at the University of London. “It seemed to me, despite my amateurish enthusiasm for art, the study of its history was based on the power of persuasion in the absence of definitive evidence. Pharmacology seemed a more realistic option,” he recalls.

As London trembled in the grip of the 1960s cultural upheaval, which shaped Western art, music, and fashion, Jessell became an eager student of neuroscience. At a time when molecular biology was still a glimmer in researchers’ eyes, drugs represented powerful tools to probe the mysteries of the human brain. “Chelsea College was situated in the heart of swinging London. I was in college, studying the effects of drugs on the brain and, at the same time, walking down King’s Road, observing the effects of drugs on the brain,” says Jessell, remembering emblematic aspects of the decade’s counterculture.

During his undergraduate years in the early 1970s, Jessell pored over scientific literature from the nascent field of neurotransmitter biology, guided by a graduate student mentor who encouraged his pursuit. With near-religious fervor, he absorbed the findings of the Swiss neurochemist Hans Thoenen, whose elegant use of brain-acting drugs showed how chemical transmission controls the nervous system’s development and function. But it was not until 1974, when Jessell arrived at the Medical Research Council pharmacology department at the University of Cambridge, where he pursued doctoral studies with neuroscientist Leslie Iversen, that he channeled his knowledge and zeal into the practice of neurobiology, the unimpeded pursuit of which has marked his four-decade career in the field.

Since the Nobel-winning demonstration of acetylcholine as the nervous system’s first chemical messenger in 1926, the field of neurotransmitters had come into its own; by the mid-1970s, researchers suspected that small peptides played similar roles in modulating electrical exchanges between nerve cells. “This became an area of intense research with a vast diversity of neuropeptides,” recalls Jessell. One such neuropeptide, discovered years earlier and dubbed substance P, turned out to be enriched in the sensory neurons of the spinal cord. “That is really where my interest in spinal cord began,” he says.

Working with Iversen, he found that substance P is released by pain-sensing nerve fibers and that opioid painkillers can suppress the release of substance P, uncovering a potential mechanism for the drugs’ analgesic action on presynaptic sensory nerve terminals, the junctions between the peripheral and central nervous systems. The findings led to Jessell’s publication of a 1977 *Nature* report, the central theme of which reappears with nostalgic periodicity throughout his research career (6). “Forty odd years later, we’re still working on presynaptic inhibition in the spinal cord, albeit in a very different way,” he recalls with ruminative wistfulness.

Doctoral degree in hand, Jessell left Britain for a brief stint in Japan before beginning a postdoctoral apprenticeship with neuroscientist Gerald Fischbach at Harvard Medical School, thanks to a Harkness fellowship that enabled Britons to experience intellectual life in the United States. When Jessell arrived at Harvard in 1978, Fischbach had been developing tissue-culture techniques to dissect the intricate process of nerve-impulse transmission across structures called synapses at the junctions of nerves and muscles. Once Jessell joined him, the pair, together with student Ruth Seigel, set about identifying the nature of a spinal cord-derived protein that triggers the synthesis and clustering of acetylcholine receptors at nerve-muscle synapses. The findings, published a year later in *Proceedings of the National Academy of Sciences USA* (7), laid the groundwork for the discovery of proteins that play constitutive roles in neuromuscular synapse development.

Evident in his early work in Fischbach’s lab, Jessell’s promise did not go unnoticed: In 1981, he gained admission to Boston’s scientific *haut monde* as an assistant professor in neurobiology at Harvard Medical School. At Harvard, he combined his deep-seated interest in sensory transmission in the spinal cord and his newfound appreciation of neural circuit development into a singular research focus on sensory systems in the spinal cord, marked by many impactful publications. Among them was a *Nature* report in which Jessell and postdoctoral fellow Craig Jahr demonstrated that ATP, the cellular energy currency, serves as a neurotransmitter in regions of the spinal cord that receive sensory nerve fibers (8).

But after four fruitful years, Jessell relinquished his position at Harvard, eager to embrace the molecular biology revolution that had begun to influence neuroscience. The appeal of New York City’s slowly expanding scientific universe, studded with star neuroscientists like Eric Kandel and Richard Axel, who
championed a molecular approach to neural science, proved hard to resist. Coupled to its intellectual ferment, the city’s rich cultural allurements, which rivaled the considerable charms of his native London, convinced Jessell to move. (Nearly two decades later, the city honored Jessell with a Mayor’s Award for Excellence in Science and Technology.)

So it was that Jessell accepted a tenured faculty position at Columbia University in 1985, commencing in earnest his now-famous work on the development and function of circuits underlying movement. The work began as an exploration of the molecular basis of spinal cord development in embryos. Toward the end of the 19th century, the Spanish anatomist Santiago Ramon y Cajal, whose graceful etchings of neural circuits loom ghostlike in the annals of brain science, volunteered a notion that neurons in the brain and spinal cord of growing embryos might be guided to their targets by diffusible molecules secreted by the targets themselves. For all its conceptual simplicity, the notion—as applied to spinal cord development—resisted certain proof for more than a century.

Until, that is, Jessell, his postdoctoral fellows Marysia Placzek and Marc Tessier-Lavigne, and Columbia University physiologist Jane Dodd devised a set of elegant experiments. Some context: The bilateral symmetry of vertebrates necessitates connections between the left and right halves of the central nervous system across a midline. In the embryonic spinal cord, neurons of the spinal commissure, which allow us to alternate and synchronize the movements of left and right limbs, are guided during development toward a midline structure called the floor plate. But precisely what guides these neurons to the floor plate had long remained a mystery.

Building on methods previously designed to unravel the push and pull of cells in the developing spinal cord, the team demonstrated that the floor-plate cells produce molecules that guide the communication cables of spinal commissural neurons to and across the midline (9). “That was a pivotal moment in our thinking about the origins of developmental pattern in the spinal cord,” says Jessell. Four years later, Tessier-Lavigne, now president of Rockefeller University, identified the molecules’ mammalian counterparts, naming them netrins after the Sanskrit word for “guide.”

The following years witnessed a wealth of findings that laid bare many secrets of spinal cord development. To wit: The position and patterning of nerve cells in the spinal cord are controlled by signals from the floor plate and an axis-defining, rod-shaped, embryonic structure called the notochord (10); a signaling protein called sonic hedgehog triggers the formation of floor-plate cells and motor neurons, which control limb movement (11); and sequential signaling by sonic hedgehog masterminds the formation of motor neurons (12). “These studies went some way to describing the overall logic of neuronal patterning and specification in the spinal cord,” Jessell says.

Moreover, the findings pointed to a network of gene switches—dubbed Hox proteins—that choreograph the delicate minuet of motor neurons and their targets in developing embryos. A group of 21 Hox proteins ensures that the scores of motor neuron types, commonly found in embryos, acquire distinct identities and connect with their target muscles in the limbs (13) (Fig. 1). Jessell and postdoctoral fellow Jeremy Dasen found that the Hox proteins in turn depend on a partner protein called forkhead box P1 (FoxP1), the levels of which determine motor neuron identity and wiring patterns. Mice lacking the FoxP1 gene, the team showed, develop a defective spinal cord, deprived of its normal diversity of motor neurons (14). “What we had managed to do with these mutant mice was to go back a few hundred million years in evolution and generate a spinal motor program that was appropriate for simple, early vertebrates like the lamprey and the hagfish. Not surprisingly, the mismatch between the evolutionarily atavistic motor system and the fully developed limbs led to profound motor dysfunction,” says Jessell.

Extending his focus on the formation of connections between motor neurons, which power muscles, and sensory neurons, which arise in muscles and relay signals back to the spinal cord, Jessell has unraveled the genetics of functional sensorimotor circuits that sustain limb movements. In 1998, Jessell and his team discovered that motor neurons and their sensory neuron targets are meticulously matched through the similarity of their gene switches, known as ETS family
proteins, which confer neuronal identity. Two years later, Jessell, his postdoctoral associate Silvia Arber, and others reported that the sensory and motor neurons of mice that lack the ETS protein Er81 failed to connect properly, resulting in severely impaired limb movement (15).

Jessell’s team has since found that motor neuron identity is not the only factor that determines their precise wiring with their sensory neuron partners: The wiring also pivots on the proper location of motor neurons in the spinal cord. Pools of motor neurons cluster and settle in discrete positions within the developing spinal cord, reflecting the positions of their target limb muscles. But in FoxP1 mutant mice, whose motor neuron pools are jumbled, the sensory neurons project to their usual positions in the spinal cord regardless of the type—or even presence—of motor neuron pools, hinting at motor neuron-independent positional cues to connectivity (16).

In the wake of such discoveries, the emerging picture provided the basis for a bold experiment: If the signals underlying motor neuron development and circuitry had been brought to light, Jessell reasoned, it must be possible to generate motor neurons from their progenitors and prod them to form circuits in a developing embryo. Around the turn of the millennium, Hynek Wichterle, a postdoctoral fellow, rose to the experiment’s challenge, coaxing mouse embryonic stem cells in lab dishes to develop into motor neurons using a couple of sequential cues—retinoic acid and sonic hedgehog—that turned the stem cells first into spinal cord progenitor cells and then into motor neurons. “When you expose mouse embryonic stem cells to the right extrinsic signals, without changing anything about their genomes, almost half the cells in that culture dish become motor neurons within a few days,” says Jessell.

Bolstered by success, Wichterle amplified his feat by inserting the embryonic stem cell-derived motor neurons into the developing spinal cord of chick embryos: The grafted motor neurons survived, integrated with the spinal cord, and reached out to their muscle targets, mimicking their natural counterparts. Hailed as a finding that could someday help regenerate human spinal cords damaged by accidents or neurodegenerative diseases, the advance in regenerative medicine was published to much praise (17). Human motor neurons have since been similarly generated from stem cells, but their successful integration into the spinal cord remains a distant dream. “Yet the therapeutic implications are clear, particularly for screening drugs that block the death of human motor neurons in diseases like spinal muscular atrophy and Lou Gehrig’s disease,” says Jessell.

To that end, Jessell has partnered with Project ALS, a New York City-based nonprofit that funds the discovery of treatments for Lou Gehrig’s disease, or amyotrophic lateral sclerosis (ALS), a form of motor neuron degeneration that often leads to progressive paralysis. “I got interested in part because Hynek’s findings suggested that suddenly you could do research on patients. Our work continues to have its basic focus, but we now have a seasoned eye to its translational implications,” Jessell says.

Together with Columbia University molecular biologist Tom Maniatis, Jessell has explored the origins of ALS by examining the genetic basis of one of its hallmarks—inflammation triggered by mutations in cells called astrocytes, which help support motor neuron function. Pursued to its logical end, the effort may influence preclinical trials of FDA-approved drugs to counter astrocyte toxicity and keep the symptoms of ALS at bay.

Therapeutic implications aside, Jessell has proffered detailed accounts of the molecular mechanics of movement that have propelled him to the forefront of his field. A testament to his preeminence, Jessell, together with fellow neuroscientists Eric Kandel, James Schwartz, and Stephen Siegelbaum, has shepherded through successive editions a touchstone textbook called *Principles of Neural Science*, arguably the most authoritative, up-to-date, and recherché account of the field to be found today.

For showing how spinal motor circuits can help link neural circuits to animal behavior and for uncovering the evolutionary underpinnings of motor neuron connectivity, Jessell has earned an array of plaudits, including fellowship in the Royal Society of London, foreign membership in the United States National Academy of Sciences, and affiliate membership in the European Molecular Biology Organization. Among the other laurels that mark his impact are a March of Dimes Prize in Developmental Biology, a Kavli Prize in Neuroscience, and Canada’s Gairdner International Award.

Despite ascending to the summit of his research area, Jessell continues to combine the pluck of a novice with the eye of an expert in the pursuit of his scientific goals, and it is perhaps to this combination of eagerness and experience that his success may be eventually ascribed. Asked what lies in store for the next decade, Jessell responds with the brio of a beginner: “Because of the developmental insights that we have distilled from the motor system, we can now begin to manipulate circuits in a mature organism with a precision that will inform us about the logic of operation of motor systems.”

In addition to Thomas Jessell, winner of the Vilcek Prize in Biomedical Science, Antonio Giraldez, Stavros Lamvardas, and Pardis Sabeti were selected from 165 applicants as winners of the 2014 Vilcek Prizes for Creative Promise in Biomedical Science. Their affiliations and accomplishments are summarized in Figure 2.
**Antonio Giraldez** (born in Spain)  
Associate Professor, Genetics, Yale University

Giraldez combines genetics, embryology, genomics, and chemical and computational biology to address a central question in biology: How does a fertilized egg develop into a complex multicellular embryo? This process requires precise spatial and temporal regulation of gene expression, and Giraldez uses zebrafish to investigate how the genome is activated and how non-coding RNAs shape gene expression during vertebrate development. Among such non-coding RNAs are microRNAs, small RNA molecules approximately 22 nucleotides in length that repress gene expression after transcription. More than 25% of the protein-coding genes. Thus, microRNAs provide a regulatory layer with potential widespread implications for development and disease. Giraldez discovered that the microRNA family, miR-430, is responsible for the clearance of maternal messenger RNAs. Giraldez has also generated zebrafish embryos with mutations in the microRNA processing machinery that affect brain, muscle and blood development, leading to the identification of novel pathways that generate these small RNAs.

**Stavros Lomvardas** (born in Greece)  
Associate Professor, Anatomy, UCSF

Lomvardas’s goal is to understand the mechanism whereby cells in the nervous system make stochastic transcriptional choices that generate cellular diversity. As a model system for his studies, he uses the mouse olfactory system, which is built upon the monoallelic expression of one out of a thousand olfactory receptor genes. Lomvardas and colleagues developed novel imaging approaches, which combined with unbiased, high throughput biochemical techniques, revealed an unprecedented network of interchromosomal interactions in the nuclei of olfactory neurons. These long-range nuclear interactions govern the singularity of olfactory receptor expression. Interchromosomal association of the inactive olfactory receptor genes, which aggregate in unique nuclear loci, assures that they remain completely silent for life, whereas interactions of the active olfactory receptor allele with distant enhancers, which occur in cis or trans, may coordinate the transcriptional activation of a single allele. In parallel with these studies, Lomvardas and colleagues investigate the role of DNA and histone methylation in olfactory receptor gene regulation and in other, disease-relevant transcriptional processes of the nervous system.

**Pardis Sabeti** (born in Iran)  
Associate Professor, Systems Biology/Immunology, Harvard University/Broad Institute of Harvard and MIT

Sabeti, a computational geneticist, studies genetic diversity by developing algorithms to detect genetic signatures of natural selection and carrying out genetic association studies. She and her colleagues probe information buried in the millions of sequence variations in the human genome, in search of signs of genome evolution. To facilitate the interpretation of large datasets, her team develops visualization tools for genomic and biomedical data, such as the software package Zye – a computational tool for the visual analysis of epidemiological data, intended to provide insight into relationships between variables within large datasets through high-dimensional data visualization. Sabeti uses next generation high-throughput sequencing technologies to create tailored sequencing pipelines for some of the world's deadliest viruses and bacteria. Using 454 and Illumina technologies, the Sabeti lab develops novel approaches to full-length genome sequencing for Lassa fever and Ebola viruses. By generating data from less than a teaspoon of blood, the team can assemble complete viral genomes for the identification and genetic analysis of known and unknown viruses.

**Figure 2.** Recipients of the 2014 Vilcek Prizes for Creative Promise in Biomedical Science. (To be considered for the prizes, candidates must not be older than 38 years of age at the time of selection).
REFERENCES


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