Profile of Alexander Y. Rudensky, winner of the 2018 Vilcek Prize in Biomedical Science

Prashant Nair^a and Jan Vilcek^{b,1}

In October 2017, the Chicago-based MacArthur Foundation announced the names of the latest winners of the renowned “genius” grants: fellowships awarded for “originality, insight, and potential,” to outstanding scientists, writers, visual artists, and members of other professions. Of the 24 fellows selected, at least one-third are immigrants to the United States, working in fields as varied as immunology, anthropology, psychology, social work, and creative writing. Foreign-born scientists in the United States are routinely well-represented among recipients of prestigious honors, including the Nobel Prizes and election to the National Academy of Sciences, to name but a couple of high honors bestowed on scientists.

In 2005, the New York City-based Vilcek Foundation began an annual prize program to recognize exceptionally accomplished foreign-born scientists working in the United States. The program’s mission is to raise public awareness of the role of immigrant talent in sustaining the nation’s global leadership in science, technology, and the arts. The Vilcek Foundation’s prize winners are chosen by accomplished peers and receive a cash award of \$100,000. Since 2009, the Vilcek Foundation has also recognized promising young scientists who have carved a niche for themselves early in their careers through pathbreaking work that has caught the attention of the scientific community; each winner of the Creative Promise Prize currently receives a \$50,000 cash award* (concomitantly, the Vilcek Foundation recognizes foreign-born artists with prizes for achievement in a different domain of artistic endeavor each year).

The 2018 Vilcek Prize in Biomedical Science is awarded to Alexander Rudensky, an immunologist at the Memorial Sloan Kettering Cancer Center and a Howard Hughes Medical Institute Investigator.

Harnessing the Reins of Immunity: Alexander Rudensky

In the fall of 2015, George Plitas was poring over data on tumor samples from breast cancer patients at the Memorial Sloan Kettering Cancer Center in New York

Alexander Y. Rudensky. Image courtesy of The Vilcek Foundation.

City. Like a clairvoyant studying tarot cards, Plitas, a breast surgeon, was looking for telltale differences from normal breast tissues. In particular, he was searching for signs that immune cells called regulatory T cells, known to initiate as T regs, were enriched in the tumors. Because their function is to keep immune responses in check, T regs are thought to blunt the efficacy of cancer immunotherapy drugs, which work by unleashing the immune system against cancer. “Some patients don’t benefit from cancer immunotherapy, so we wanted to understand whether this was partly because of the density of these cells in the tumor,” explains Plitas.

Sure enough, Plitas found more T regs in the tumors than in blood and normal breast tissues; the more aggressive the tumor, the higher the level of T regs (1). Intriguingly, the tumor-dwelling T regs sported higher-than-normal levels of a protein on their surface called CCR8, raising the tantalizing hope that the cells could be singled out and suppressed. The finding spurred an ongoing search for ways to target CCR8, deplete or override T regs, and allow immunotherapy drugs to beat back tumors. Plitas’ finding

^aProceedings of the National Academy of Sciences USA, Washington, DC 20418; and ^bDepartment of Microbiology, New York University School of Medicine, NYU Langone Medical Center, New York, NY 10016

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¹To whom correspondence should be addressed. Email: jan.vilcek@nyumc.org.

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T regs in the T cell zone of a lymph node. Foxp3 is shown in blue, CD4 in green, T-bet in red, and CD44 in white. Image courtesy of Alejandra Mendoza (Memorial Sloan Kettering Cancer Center, New York City).

was built on a decade's worth of discoveries by his scientific mentor Alexander Rudensky, who had described the identity of T regs in minute molecular detail. Over the course of a distinguished career, Rudensky, an immunologist at Memorial Sloan Kettering Cancer Center, a member of the National Academy of Sciences, and winner of the 2018 Vilcek Prize in Biomedical Science, has uncovered molecular mechanisms underlying the immune system's role in autoimmunity, infectious diseases, and cancer.

Westward Bound

To recount Rudensky's childhood is to conjure life in the Soviet Union in the early 1960s, a decade at once marked by political tumult and scientific progress; Soviet leader Nikita Khrushchev had installed midrange nuclear missiles in Cuba that were pointed at the United States, and cosmonaut Yuri Gagarin had orbited the Earth in the first manned spaceflight. Against this backdrop, Rudensky, who was born in Moscow to Jewish intellectuals during the Khrushchev years (his father was a Soviet army officer turned engineer, and his mother studied law and Russian literature) became enamored with science. "Back then, natural sciences were less influenced by Soviet propaganda than other disciplines," he recalls. So he followed a meandering path through mathematics, botany, and chemistry before settling on biochemistry. Upon graduating from high school, he studied biochemistry at Moscow's Second Medical School, where he embarked on a Master's thesis project, mapping the interaction of a bacterial protein with an antibody. Rudensky's polymath ability to move through scientific fields would prove useful in later years, when his interest was consumed by a type of immune cell with functions so diverse it appears to influence almost every aspect of immunity.

Energized by his exposure to experimental immunology, Rudensky joined Vitalij Yurin at Moscow's Institute for Genetics of Microorganisms in 1979. There, he studied the molecular basis of the interplay between the immune system's principal players, called T cells,

and its handmaidens, called B cells, which produce antibodies and help prime the former for immune defense against pathogens. His doctoral work led to a series of articles in the *European Journal of Immunology* (2, 3), a veritable coup for a Soviet scientist, but Rudensky longed to expand his horizons.

Fortunately, with the rise of Mikhail Gorbachev and the fall of the Berlin Wall in the late 1980s, political change swept through the region, parting the Iron Curtain. In 1989, Rudensky traveled to Germany to present his scientific work. By then, the United States had become the nerve center of the global scientific enterprise, and he messengered a letter to Yale University addressed to Charles Janeway, who counts among the world's most garlanded immunologists and was known for guiding the careers of young scientists. Rudensky could hardly believe his luck when his missive was met with a nod. Asked for his thoughts on what prompted Janeway to welcome an untested inconnu to Yale, Rudensky jests, "I think it was collector's instinct. Charlie had flags from different countries on the walls, and he hadn't had a postdoc from the Soviet Union."

In the winter of 1990, with his pregnant wife and three children in tow, Rudensky left Moscow for the ivy-clad halls of New Haven. In Janeway's laboratory, extending his earlier work on antigen presentation in the immune system, he set forth to sequence fragments of cellular antigens bound to proteins called major histocompatibility complex class II molecules. The work, published in *Nature* (4), uncovered crucial insights into the mechanisms by which the immune system distinguishes self from nonself, placing Rudensky squarely in the pantheon of modern immunology. Two years later, with Janeway's support, he accepted an assistant professorship at the University of Washington in Seattle. "It was an exciting, closely knit, young immunology department with handpicked faculty in a beautiful city," he says.

Tryst with T Regs

In Seattle, antigen presentation remained the major focus of his research group, marking his meridian years. But he soon lasered in on T cells, and it is this lateral branch of his lab's work that became the leit-motif of Rudensky's research. In the late 1980s, Japanese researcher Shimon Sakaguchi had described a group of helper T cells whose surfaces are embellished with a protein called CD25 (5). These cells appeared to tamp down overzealous immune responses that occur when the immune system mistakes the body's own proteins for interlopers. For their role in averting potentially catastrophic autoimmunity, this group of cells had earned the moniker T regs, or regulatory T cells. But whether these cells represented a distinct lineage or merely a transient state of activated T cells remained unclear. Meanwhile, immunologist Fred Ramsdell, now at the Parker Institute for Cancer Immunotherapy in San Francisco, found that the autoimmunity observed in a strain of mutant mice housed at Oak Ridge National Laboratory in Tennessee could be attributed to mutations in a gene switch called Foxp3 (6); other researchers had reported that the gene switch was mutated in

patients suffering from a rare, potentially fatal genetic disorder called IPEX syndrome, which is marked by autoimmunity and often requires bone marrow transplantation (7).

Together with graduate student Jason Fontenot and postdoctoral associate Marc Gavin, Rudensky attempted to braid those disparate strands of evidence into a coherent narrative, hoping to uncover genetic factors that govern the development of T regs. Before long, the trio found that mice lacking *Foxp3* were deficient in T regs; conversely, infusing T regs into the mutant mice countered autoimmunity. Together, these observations hinted obliquely at *Foxp3*'s central role in T reg development. When the team demonstrated that engineering *Foxp3* into helper T cells lacking the CD25 protein, a trademark feature of T regs, endowed them with T reg-like immunosuppressive properties, the case that *Foxp3* controls and confers T reg identity was clinched. Fittingly, Rudensky, Sakaguchi, and Ramsdell shared the 2017 Crafoord Prize in polyarthritis research, jointly awarded by the Royal Swedish Academy of Sciences and the Crafoord Foundation.

Rudensky's report on *Foxp3*, published in *Nature Immunology* in 2003, was proclaimed a classic (8, 9). With the serene self-assurance that comes from making a solid discovery, he explains why the description of a genetically distinct subpopulation of T cells controlling autoimmunity captivated immunologists: "It was a rare and striking example in biology of dominant negative regulation acting *in trans*." In other words, the findings bolstered the notion that the immune system has evolved a dedicated group of cells whose *raison d'être* is to tame other immune cells.

Immunity's Factotum

As his interest in T regs deepened, Rudensky came to grips with the vast panoply of roles they play in the immune system, beginning as early as the conception of life. Pregnancy poses a quandary to the maternal immune system because fetuses are studded with paternal antigens, which can trigger adverse immune responses. Previous studies had found that experimentally depleting T regs in pregnant mice resulted in the resorption of embryos and termination of pregnancy. Meanwhile, reports of decreased numbers of T regs in women who had inexplicably suffered pre-eclampsia and repeated miscarriages began to surface. Together, the observations suggested a role for T regs in protecting growing embryos from attack by the maternal immune system. Probing the link, Rudensky's team found that placental mammals have evolved a snippet of DNA in their genomes called the CNS1 enhancer, which boosts the expression of *Foxp3*. Together, CNS1 and *Foxp3*, the team found, can trigger the formation of T regs in the body's peripheral tissues; the major source of T regs in the body is the thymus gland, a pyramid-shaped organ that sits beneath the breastbone. The peripheral T regs, in turn, rein in the maternal immune system's reflexive attack on paternal antigens in growing embryos, thus resolving potential conflicts between mother and fetus and keeping spontaneous miscarriage at bay. With this discovery,

Immunohistochemical staining of a human triple-negative breast cancer tumor with anti-*Foxp3* antibody (brown) and hematoxylin. Image courtesy of Hannah Y. Wen (Memorial Sloan Kettering Cancer Center, New York City).

published in *Cell* in 2012 (10), Rudensky established the primacy of T regs in early human development.

Reinforcing their widespread role in human physiology, Rudensky and his coworkers reported in *Nature* that peripheral T regs communicate with intestinal microbes to keep gut inflammation under control (11). Previous studies had hinted that some microbes that inhabit the human gut trigger the generation of inflammation-dowsing T regs, while others boost inflammation-inducing T helper 17 cells. A delicate balance between the two cell types is crucial to maintaining gut health. But the molecular nature of this chatter between gut microbes and the immune system remained undeciphered. Rudensky's team transplanted gut microbial metabolites between strains of mice with defined compositions of gut microbes. The experiments revealed that the microbial fatty acids butyrate and propionate boosted the generation of peripheral T regs, a process dependent on the CNS1 enhancer previously shown to activate *Foxp3*. The findings led to an emerging picture of how chemical signals produced by bacteria orchestrate the interplay of gut microbes and the immune system, ensuring harmony between mechanisms that boost and block inflammation. This work is bound to illuminate the immune system's role in allergies and inflammatory disorders, says Rudensky.

Proving the point, two years later, Rudensky's team ferreted out yet another vital function performed by T regs: T regs actively promote the maintenance and repair of tissues damaged by inflammation through a dedicated mechanism. Centered on a molecule called amphiregulin, which is secreted by T regs in lung, adipose, and intestinal tissues, this mechanism is triggered upon tissue damage. When the team removed the gene for amphiregulin from T regs, mice exposed to the flu virus suffered severe acute lung damage, despite mounting normal antiviral immune responses (12).

The findings diversified the portfolio of T regs and demonstrated that they function as a factotum in the immune system. "The hope is that this will inspire better treatments for diverse diseases marked by loss of tissue function," says Rudensky.

T regs, Front and Center

In 2008, Rudensky was lured back east with an offer from Memorial Sloan Kettering Cancer Center in New York City that he readily accepted. At Sloan Kettering, where he applies his work on T regs to cancer treatment, he eventually succeeded immunologist James Allison as chair of the immunology program and director of the Ludwig Center for Cancer Immunotherapy when Allison left for his current home in Houston.

Eight years after his arrival at Sloan Kettering, Rudensky unveiled how T regs that infiltrate tumors thwart cancer immunotherapy drugs, impeding treatment. His initial studies had indicated that transiently depleting T regs in a mouse model of aggressive breast cancer delayed tumor progression and metastasis (13). Together with Plitas, graduate student Kasia Konopacki, and others, Rudensky set about translating those observations for human breast cancer treatment. The team compared T regs in human mammary glands with their brethren that clustered within patients' untreated breast cancer tissues, finding that the latter group

squelched the antitumor action of other immune cells more aggressively than the former. Close inspection revealed that genes encoding receptors for immune molecules called chemokines appeared to be in overdrive in tumor-dwelling T regs. In particular, T regs in tumors were enriched in the chemokine receptor CCR8, and patients with elevated CCR8 had relatively poor outcomes, suggesting that targeting CCR8 might enhance the efficacy of immunotherapy, particularly immune checkpoint blockade, for breast cancer. Rudensky and Plitas plan to develop and test antibodies that can bind to and gum up CCR8. The hope is that such an intervention will throw a wrench in the immunosuppressive action of T regs, giving immunotherapy a fighting chance against cancer.

Contemplating the future, Rudensky says the forthcoming years of research on T regs are bound to be prolific, paving the way for innovative treatments for cancer, inflammation, and autoimmune disorders. If the unremitting spate of articles on the topic is any indication, his pronouncement might prove prophetic.

*The 2018 Vilcek Prize for Creative Promise in Biomedical Science is awarded to Massachusetts Institute of Technology (MIT) material scientist Polina Anikeeva (from Russia), Stanford University neuroscientist Sergiu Pasca (from Romania), and Broad Institute of MIT and Harvard molecular biologist Feng Zhang (from China).

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