Alex Proekt, M.D., Ph.D., Recipient of the 2021 James E. Cottrell, M.D., Presidential Scholar Award

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From Russia with love: The 2021 recipient of the James E. Cottrell, M.D., Presidential Scholar Award is Alex Proekt, M.D., Ph.D. Alex's meteoric rise to a newly tenured Associate Professor of Anesthesiology at the University of Pennsylvania, Perelman School of Medicine (Philadelphia, Pennsylvania), will come as no surprise to those who know him. As a 13-yr-old, Alex moved with his parents and brother from St. Petersburg, Russia, to the United States. Alex's STEM foundations were solidified at Carnegie Mellon University (Pittsburgh, Pennsylvania), where he majored in biological sciences. Alex completed dual degree training at Mount Sinai School of Medicine (New York, New York), receiving his M.D. and neuroscience Ph.D. degrees. Anesthesiology was fortunate to attract Alex. At Weill Cornell Medicine (New York, New York), Alex entered the Van Poznak combined anesthesiology research residency scholar's track. Under the direction of John Savarese, M.D., and then Hugh Hemmings, M.D., Ph.D., Alex honed his clinical skill set while simultaneously working with Don Pfaff, Ph.D., and Marcelo Magnasco, Ph.D., at The Rockefeller University (New York, New York), rising through the residency and then joining the faculty at Cornell before moving to the University of Pennsylvania in 2015.

Under a variety of settings that span the full breadth of the academic quadripartite mission from ground-breaking science, to stellar clinical care, to outstanding teaching, and finally to splendid mentoring of medical students, graduate students, residents, and most recently, newly minted junior faculty, Dr. Alex Proekt shines. He is a rising star in anesthesiology who is most deserving of this prestigious award. Alex embodies the very best academic anesthesia offers. Both inside and outside of his home institution, many have noted Alex possesses one of the sharpest minds in his generation.

Proekt has already made considerable advances to our understanding of the anesthetized brain and the way in which it transitions to and from states of unconsciousness. In a seminal paper he published in the *Proceedings of the National Academy of Sciences USA* in 2014,[1] Alex demonstrated that the anesthetized brain does not slowly or continuously climb out of the abyss of general anesthesia as an anesthetic is progressively decreased. Rather, he has conclusively proven that the rodent brain makes a series of hops among metastable intermediate states, jumping abruptly and discontinuously from burst suppression to delta-dominant states and then again from delta-dominant to faster rhythms. Critically, such transitions only occur from a subset of permissible states through which the brain must first pass on the journey back to wakefulness. Alex has confirmed his rodent data in healthy humans. In another landmark publication, Alex demonstrated that the amount of time volunteers spend in burst suppression does not correlate either with the time required to emerge from a 3-h, deep isoflurane anesthetic, or with the return of higher cognitive function.[2] These human data fit nicely with his framework suggesting that the brain must stochastically leap from one metastable intermediate to another and does not continuously ascend from a "depth." This precise question of how transitions occur mechanistically is the subject of Alex's first National Institutes of Health (Bethesda, Maryland) R01 grant, "The Neurophysiological Mechanisms of Recovery of Consciousness," which follows on his successful Foundation for Anesthesia Education and Research Mentored Research Training Grant and National Institutes of Health K08 grants. Alex's work changes the way we should think about the depth of anesthesia.

Keeping sight of the central question for all of neuroscience and perhaps the single question that enables all of research, Alex's research asks, "How and why are we conscious?" Alex has devised several exceedingly clever analyses applied from the fields of dynamical systems theory and applied physics and has translated them to the electroencephalogram (EEG) and electrocorticogram in both awake and anesthetized rodents, monkeys, and humans. In his investigations about how the conscious brain is able to perceive and respond to stimuli, Alex has demonstrated that the awake brain operates on the razor's edge, precisely at the point of dynamic criticality.[3,4] The elegance of Alex's mathematical insights has made us wonder why it has taken so long for these concepts to be applied. Were the brain to be "too stable," electrical activity induced by any perturbation would rapidly dampen—potentially without leading to neural circuit or behavioral adaptations in the individual. Conversely, were the brain "too unstable," then any tiny perturbation would permanently disrupt ongoing

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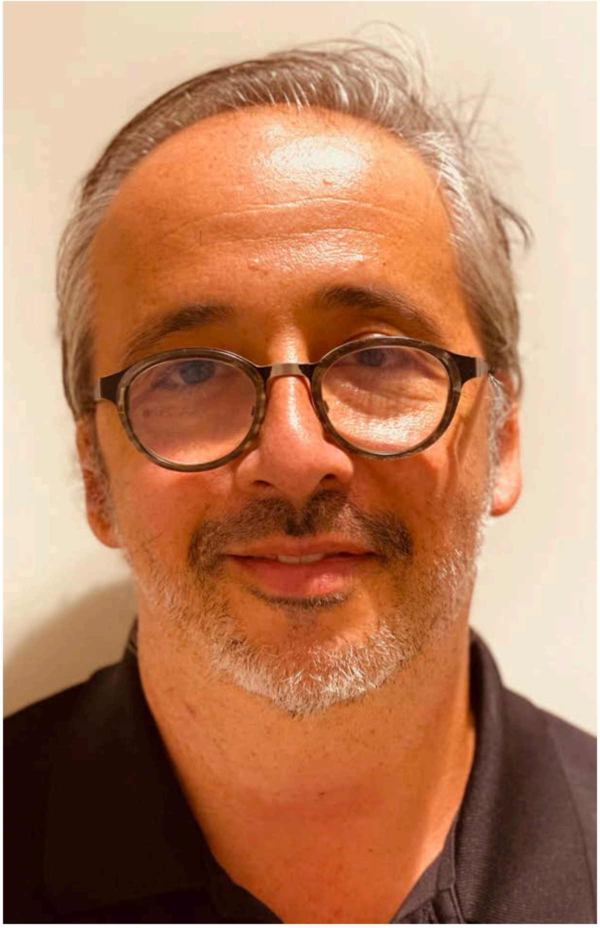

electrical activity to adversely affect circuit and behavioral function. The beauty of Alex's discovery is that he has proven what has been in front of all neuroscientists since Hans Berger first demonstrated the characteristic oscillations of the human EEG nearly 100 yr ago. Alex has supplied modern neuroscientists with a new set of tools to analyze the rhythms underlying conscious perception. He has proven with distinct general anesthetics that the unconscious state occurs with a loss of dynamic criticality and has mapped the way forward for basic scientists, neurologists who study disorders of consciousness, and anesthesiologists attempting to prevent awareness under anesthesia. Moreover, this question of using dynamic stability to predict the responsiveness of the human brain to stimuli is the subject of Alex's second R01 grant, "The Role of Dynamic Criticality in Human Perception."

Alex's research has also opened a novel window into the actions of general anesthetics in individuals and not just in populations of individuals. Moving beyond the traditional notion of the population EC_{50}, Alex has uncovered a novel explanation for anesthetic hysteresis—resistance to state change. This measure can be quantified in individuals, is stable across time in individuals, and is common both to zebrafish and mice. Given the 400 million yr of evolutionary distance between these vertebrates, all evidence suggests that resistance to state transitions is likely conserved in the human brain as well. The implications of Alex's most recent publications[5–9] argue that resistance to state transitions might provide a novel explanation for pathologic reconstitution of consciousness. At one extreme, too little resistance could lead to unwanted awareness under anesthesia. At the other, delayed and disorderly reassembly may culminate in emergence delirium as the formerly anesthetized brain jumps to an unfavorable yet metastable intermediate state of near-wakefulness.

Probing deeper into the question of how neural activity drives behavior, Alex showcased his expertise as a systems and computational neuroscientist. Using publicly available whole brain imaging data from the worm *Caenorhabditis elegans*, Alex has successfully uncovered a heretofore unrecognized feature of neuronal dynamics. This novel methodology has enabled Alex to make predictions of future behaviors—not just in a single worm. Having solved the behavioral control loops, he can apply the dynamics to predict impending behavior in unrelated worms. The astounding results from the Proekt lab demonstrate that predictions based solely on neural activity fail.[10] Rather, it is the trajectory of changes in neural activity that appears critical in predicting behavior in worms—and in a manuscript currently under review at *Neuron*—in monkeys and humans as well.

Since he has been an Assistant Professor at the University of Pennsylvania, word of Alex's brilliance has spread across the campus. He is a highly sought-after Ph.D. mentor. He is currently serving as the primary Ph.D. advisor to three neuroscience graduate students and is a co-advisor to a fourth M.D. Ph.D. student. Two of his graduate students have been awarded with National Institutes of Health F30/F31 individual training grants. His third won a prestigious Google Fellowship Award for computational neuroscientific studies. Alex is also on the Ph.D. committees of six other graduate students. He helps to increase the prominence of anesthesiology beyond its traditional reaches in the operating rooms through his service as an M.D. Ph.D. admissions committee member and lecturer to the medical and graduate schools at the University of Pennsylvania. Perhaps more importantly, Alex has been invited to lecture nationally within the anesthesia departments at Massachusetts General Hospital (Boston, Massachusetts), University of Wisconsin (Madison, Wisconsin), New York University (New York, New York), Duke University (Durham, North Carolina), University of Washington (Seattle, Washington), and Johns Hopkins University (Baltimore, Maryland), and internationally at a University of Waikato conference held in Queenstown, New Zealand, at the European Institute for Theoretical Neuroscience in Paris, France, at the Israeli Society of Anesthesiologists in Tel Aviv, Israel, and at the Department of Physics in Vrije Universiteit Amsterdam, The Netherlands.

In the operating rooms at the University of Pennsylvania, Alex is a prized teacher to residents and medical students. He has consistently scored among the highest rated attendings in the department since his arrival on our faculty in 2015. Alex has been a mentor to several Foundation for Anesthesia Education and Research Medical Student Anesthesia Research Fellows. His two most recent students, Cameron Bosinski (2018) and Tiffany Tse (2019), each won Foundation for Anesthesia Education and Research medical student and resident scholar research symposium awards for their projects in successive years at Anesthesiology. Alex serves as a co-mentor to members of our Dripps research track residency, including Vicki Bedell, M.D., Ph.D., Railey White, M.D., Ph.D., and Joseph Cichon, M.D., Ph.D., all of whom recently joined our faculty as newly minted tenure track assistant professors in July 2021.

As a clinician scientist who spends 25 to 35% of his time as a neuroanesthesiologist, caring for patients who present with pathology of the brain and spine, Alex is also sought after clinically. He is a prized physician with much to add to resident education and patient care. Not surprisingly, Alex's intraoperative EEG teaching is unparalleled.[11] Moreover, his deep understanding of neurophysiology and the implications of distinct anesthetic drugs makes him invaluable to our neurosurgeons, whether for implanting deep brain electrodes for the treatment of intractable epilepsy, performing awake craniotomies that require a predictable and prompt return to consciousness during intraoperative tumor mapping, or complex repair of cerebral aneurysms.

For all of these reasons, Dr. Alex Proekt is a phenomenal choice for the James E. Cottrell, M.D., Presidential Scholar Award. His research contributions in model organisms ranging from *Aplysia* to worms, zebrafish, fruit flies, mice, rats, monkeys, and humans enable Alex to ask fundamental questions and translate discoveries across nearly every living model organism. In our more than 50 yr collectively in science at Yale University (New Haven, Connecticut), the University of Pennsylvania, and Harvard University (Cambridge, Massachusetts), we have never met a more insightful scientist, capable of translating physics, mathematics, data science, physiology, and biology to anesthesiology. His work has been published in high-impact journals such as *Nature Communications,*[12] *eLife,*[5,10] *Proceedings of the National Academy of Sciences USA,*[1,13,14] *Journal of Neuroscience*,[3,15] and our top journals in anesthesiology. With two current R01 grants and another presently under review at the National Institutes of Health, Dr. Alex Proekt is helping to transform anesthesiology science and practice. We can think of no one more qualified for this prestigious award.

Competing Interests

The authors declare no competing interests.

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