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Alexei Verkhratsky: From neuroglial pathophysiology to therapeutic strategies for brain disorders

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Professor Alexei Verkhratsky revolutionizes our understanding of neuroglia through groundbreaking research that transforms how we view brain disorders and therapeutic possibilities. This illuminating Genomic Press Interview reveals the extraordinary journey of an internationally acclaimed neurophysiologist whose pioneering discoveries in neuroglial pathophysiology have fundamentally reshaped neuroscience. Born in Ukraine and now at the University of Manchester, Verkhratsky stands as a towering figure with over 600 publications, including landmark articles on glial ionic excitability, astroglial sodium signalling, and pathophysiology of neuroglia that fundamentally changed our understanding of brain function in health and disease. His election to prestigious academies, including the German National Academy of Sciences Leopoldina, Academia Europaea, and multiple European academies, underscores his profound scientific impact. Verkhratsky's revolutionary work discovered that while neurons communicate through electrical impulses, glial cells possess specific form of intracellular excitability mediated by dynamic changes in ions and second messengers, demonstrating that glia actively participate in brain information processing through neurotransmitter receptors and calcium waves rather than being passive support cells. This paradigm-shifting concept of glial calcium excitability revealed an entirely new dimension of brain communication. His groundbreaking research on neuroglial ionic signalling, including sodium and chloride mechanisms, provides crucial insights for developing therapeutic strategies. As Professor of Neurophysiology in Manchester and through distinguished professorships worldwide, he champions the view that neuroglial malfunction drives brain disorders including neuropsychiatric and neurodegenerative diseases. His comprehensive 730-page reference book on neuroglia, published in 2023 with Arthur Butt, represents the culmination of decades of transformative research. Through extensive international collaborations and mentorship, Verkhratsky continues advancing neurogliopathology, offering hope for treating depression, Alzheimer's disease, multiple sclerosis, and other devastating brain disorders by targeting neuroglial homeostatic support and neuroprotection mechanisms.

Figure 1. Alexei Verkhratsky, MD, PhD, D.Sc, ML, MAE, MRANF, MPAS, MSASA, The University of Manchester, UK.

Part 1: Alexei Verkhratsky – Life and Career

Where were you born, and where do you live now?

I was born in Ukraine, in the city of Stanislav (Western Ukraine; now Ivano-Frankivsk); currently, I live in Manchester, UK.

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I was born into a family of medics and academics; from an early age, I was exposed to medicine and research. My grandfather, besides being a renown surgeon, was also a prominent historian of medicine, and this ignited my passion for history. I educated myself in medicine at Kiev Medical University and studied history simultaneously on my own accord – this was the only choice because in the Soviet Union, history was the instrument of propaganda and indoctrination; hence, formal studies were not for me. During the first year of medical university, I read two books – "The Conduction of the Nervous Impulse" by Alan Hodgkin and "The Physiology of Synapses" by John Eccles. Their insights into the cellular mechanisms of the brain function fascinated me, and a year later, in 1979, I approached Platon Kostyuk, who led the Bogomoletz Institute of Physiology in Kiev; at that time, this institute was a prominent centre in cellular physiology of the nervous system.

Those were exciting days when the quest for single channels culminated in the perfection of the patch-clamp technique. In Kiev in 1972, Oleg Krishtal and Volodymyr Pidopliche developed the method for intracellular perfusion in combination with voltage-clamp, which was one of the precursors for patch-clamp. For a decade that followed, almost all major figures in electrophysiology were visiting Kiev. Therefore, I was able

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to meet Bert Sakmann, Ervin Neher, Ole Petersen, Beril Hille, to name but a few. These meetings were highly motivating and instrumental in shaping my views and ideas. After graduating as a medical doctor, I entered a PhD program at Bogomoletz Institute of Physiology to study ionic currents in cardiomyocytes. The degree was duly obtained, but more importantly, I learned electrophysiological techniques at their source.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

I was introduced to the field of neuroglia 36 years ago by Helmut Kettenmann, who invited me to stay in his laboratory in Heidelberg, to which I arrived in early October 1989. Neuroglia was not much popular in those days; probably fewer than 40 laboratories around the world were engaged in studies of these cells. I was lucky again because Helmut was one of the most prominent figures in the field; incidentally, in 1988, he (together with Bruce Ransom) started the journal GLIA, which has been shaping neuroglial research since. In addition, Helmut is a keen historian, and he collected a unique library on neuroscience and neuroglia, including early publications by Rudolf Virchow, Karl Weigert, Karl-Ludwig Schleich, Max Schulze, and many more. I embraced neuroglia with all the passion of a neophyte.

For next two decades I busily studied all types of neuroglia, including oligodendroglial cells and their precursors (incidentally my first neuroglial paper published in 1990 in *Neuroscience Letters* (Verkhratsky AN et al. *Neurosci Lett* 1990. DOI: 10.1016/0304-3940(90)90202-k), reported the discovery of 2 types of voltage-gated calcium channels in these precursors, generally known as OPCs; they are eccentric neuroglia because many of them are electrically excitable and can generate action potentials; they also receive neuronal synaptic inputs), peripheral Schwann cells, microglia and astrocytes. Yet I was a medical doctor in my soul, and I always thought about pathology. In 2010, I started to look at neuroglia in various diseases, and soon I realised that (contrary to the dominating idea of the prevalence of reactive gliosis and neuroglial toxicity driving neuronal tissue damage) in many, if not all, brain diseases, as well as in ageing, neuroglia undergo atrophy and functional asthenia. Loss of neuroglial homeostatic support and neuroprotection are the main factors triggering and propagating the damage of the nervous tissue.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channelled you toward that leadership responsibility?

Throughout my scientific life, I have always sought extensive collaborations that widened my comprehension and perspective; I dedicated considerable effort to investigating mechanisms of calcium signalling in various contexts and to purinergic neurotransmission. Both are, incidentally, prominently present in neuroglia and contribute to neuroglial excitability, which, in contrast to neurones, is not supported by excitable plasmalemma but relies on changes in intracellular ions and second messengers. Through collaboration, I met many remarkable academics, of whom Geoff Burnstock particularly influenced my evolution; we also developed a close friendship that lasted till he passed away in 2020. Collaboration also had a massive cultural influence: for example, for 10 years, I was in Japan, at Kyushu University for a month every year, teaching students and working in the laboratory of another close friend, Mami Noda. I got infatuated with Japanese culture, and started collecting Japanese woodblocks (see Figure 2), the famous ukiyo-e (images of the floating world), and learned a bit of calligraphy (every New Year, I spend a couple of days designing a kakizome – the kanji of the year). In recent years, I work closely with several outstanding young Chinese researchers, and I am trying my best to convey to them my experience and knowledge – very rewarding indeed. I spend a significant amount of time in China, not only conducting research, but also learning about the country's history and culture – and practicing calligraphy even more.

What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

My only "mistake" was being born in the Soviet Union. On one hand, it cost me 35 years of my life; on the other, it gave me an intimate understanding of that system from within—and my God, how horrible it was (and remains in Muscovy today). This experience rendered me permanently immune to the allure of communism, socialism, and similar ideologies.

Figure 2. Japanese woodblock print (shin-hanga) from Alexei Verkhratsky's collection: Takahashi Shotei (高橋松亭), *Nichiren in the Snow on a Mountain Path*, 1936. Nichiren was a Japanese Buddhist priest who founded the Nichiren school of Buddhism. Like the solitary figure traversing a snowy path, scientific inquiry often requires perseverance through challenging conditions, yet the knowledge gained makes the journey profoundly rewarding.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

I double and triple check everything, citing only those papers that I read and never relying on secondary sources.

Please tell us more about your current scholarly focal points within your chosen field of science.

My main focus is on neuroglial pathophysiology across a wide range of diseases; I study neuropsychiatric disorders, brain trauma, autoimmune pathologies such as multiple sclerosis and neuromyelinitos optica, cerebral small vessels disease, stroke, and chronic pain; I even do some research into traditional Chinese medicine, which is quite enlightening from historic, cultural and therapeutic perspective. In short, I aim to find a cure for the disturbed brain, which requires characterising the underlying pathophysiological mechanism. Knowing pathophysiology makes finding the cure a technical issue, which still may take decades and massive efforts, but knowing what to search for is fundamental.

What impact do you hope to achieve in your field by focusing on specific research topics?

I do not focus on a specific research topic; instead, I try to explore as many as possible – this makes life exciting. Of course, my research stays mainly within the neuroglial field. However, I am involved in a relatively wide range of different projects, from cellular and molecular mechanisms to

clinical studies. In addition, I also dive into the history of medicine and neuroscience.

What do you most enjoy in your capacity as an academic or research leader?
Sharing knowledge with my colleagues and students.

At Genomic Press, we prioritize fostering research endeavours based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that you feel strongly devoted to?
What is meant by this question: the essence of science is the generation of new knowledge, and this embraces it all.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?
Books, music, art, and travel; I travel with my wife, and this gives us lots of memorable and pleasant moments.

Part 2: Alexei Verkhratsky – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
Curiosity.

Among your talents, which one(s) give(s) you a competitive edge?
Perseverance and breadth of knowledge.

If you could change one thing about yourself, what would it be?
I have never asked myself such a question, but most likely nothing.

What is your current state of mind?
Anxious – the world is entering WWIII and seems relatively relaxed about it. Unless barbaric Russia is *viribus unitis* defeated, we shall see a catastrophic downfall of our world, including science.

What is your idea of perfect happiness?
Ivory tower with books, arts, and music.

When and where were you happiest? And why were so happy then?
I really do not know the answer. I had many moments of happiness, each unique in its own way, making it difficult to choose one.

What is your greatest fear?
At my age, I do not have much to fear.

"If it be now, 'tis not to come; if it be not to come, it will be now; if it be not now, yet it will come: the readiness is all: since no man knows aught of what he leaves, what is't to leave betimes?" — William Shakespeare, *Hamlet, Prince of Denmark*, Act V, Scene 2 (c. 1600-1601)

What is your greatest regret?
None.

What are you most proud of?
I must admit I do not entertain such a feeling.

What do you consider your greatest achievement?
Writing and publishing (together with my friend Arthur Butt) in 2023, the most comprehensive reference book on neuroglia – 730 pages of glial history, function, and pathology.

What or who is your greatest passion?
Reading, opera, classical music, multicultural gastronomy, collecting books and antiques, and many more.

What is your favourite occupation (or activity)?
Enjoying life (of note, science is part of this joy).

What is your greatest extravagance?
I prefer to keep this to myself.

What is your most treasured possession?
My library, family archives, and my art collection.

Where would you most like to live?
Venice.

What is the quality you most admire in people?
Knowledge.

What is the trait you most dislike in people?
Lack of interest.

What do you consider the most overrated virtue?
A virtue cannot be overrated.

What do you most value in your friends?
Loyalty and knowledge.

Which living person do you most admire?
My wife.

Who are your heroes in real life?
None.

If you could have dinner with any historical figure, who would it be and why?
I am not sure I would like to see figures from bygone days in flesh.

Who are your favourite writers?
Shakespeare, Dante, Stern, Gibbon, Mommsen, Montaigne, and Rabelais.

Who are your heroes of fiction?
Difficult to choose; I love Uncle Toby, though.

What aphorism or motto best encapsulates your life philosophy?
Carpe Diem[2]

[1] In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for $130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

[2] "*Carpe Diem*" comes from Horace's *Odes* (23 BC). Though commonly translated as "seize the day," it literally means "pluck the day" – a horticultural metaphor about harvesting life's moments as they ripen, reflecting Horace's Epicurean philosophy of mindful moderation rather than aggressive action.

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