

**INNOVATORS & IDEAS: RESEARCH LEADER**

## Peter W. Kalivas: To the tetrapartite synapse and beyond – A pathway for new drug targets to treat behavioral disorders

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**Peter Kalivas stands as a pioneering architect in our understanding of addiction neuroscience, having transformed our knowledge of how substances of abuse reshape brain circuits and cellular function. Over four decades, his groundbreaking research has illuminated the fundamental mechanisms underlying substance use disorders, mainly through his seminal discoveries of glutamate’s critical role in addiction and his innovative work on the “tetrapartite synapse” – revealing how astroglia and the extracellular matrix regulate addictive behaviors. With over 400 publications and eight edited volumes, his research has revolutionized our conceptual framework for treating addiction by identifying novel therapeutic targets beyond traditional neurotransmitter systems. After receiving his PhD in Pharmacology from the University of Washington and completing postdoctoral training at the University of North Carolina, Dr. Kalivas built an extraordinary scientific legacy at Washington State University and then as the founding Chair of Neuroscience at the Medical University of South Carolina. There, he established a world-renowned research program that has trained generations of addiction scientists while developing innovative approaches to understanding stress, PTSD, and substance use disorders. Now serving as Distinguished University Professor, he continues to pioneer new frontiers in addiction neuroscience through his work on neural circuits and synaptic plasticity. In this Genomic Press Interview, Dr. Kalivas shares insights from his remarkable journey investigating the neurobiology of addiction and his vision for the field’s future.**

### Part 1: Peter W. Kalivas – Life and Career

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

My Dad was a physician in private practice who brought home a microscope and histology from various tissues for me in the 4<sup>th</sup> grade. I was already interested in science, but this kindled my interest in biology. The other big influence was the Golden Book Encyclopedia I avidly read cover to cover in grammar school as each issue came out.

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

Leadership was not my goal, at least not consciously. That said, as a professor at Washington State University’s School of Veterinary Medicine, I was isolated and falling behind my colleagues at institutions with a larger critical mass in researching substance use disorder. In the late 1990s, I looked at endowed chair positions and decided to interview in Charleston for an open Chair of Physiology. Growing up in Los Angeles, I found the idea of being on the coast in a warm place appealing but running a department was not so appealing. However, Charleston came together with



**Figure 1.** Peter Kalivas, PhD, Medical University of South Carolina, USA.

an excellent start-up opportunity to build a Department of Neuroscience where I could create a critical mass of research faculty. Equally important, Sue (my wife) and I agreed that it would be a great place to live and finish raising our kids. We were on a 10-year plan that is now in its 25<sup>th</sup> year.

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

I was initially focused on environmental science as a college sophomore, but after reading the *Ghost in the Machine* by Arthur Koestler who introduced me to Robert MacClean’s ideas of schizophychology I became interested in how the brain functions. About the same time I did a term paper on the work by Conrad Waddington who first coined the term epigenetics as a way to bridge Darwin and Lamarck. Together, these moved me towards a career in neuroscience.



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

My hopes have changed over my career from grandiose early on to more practical as time went by. Initially (as an undergraduate), I wanted to figure out mechanistically how the brain creates emotions, spiritual feelings, and thoughts. This tilted towards less grandiose goals related to how psychotropic drugs affect the brain as I came to personally experiment with various mind-altering substances. As with most of us in the early days of neuroscience, I gradually settled on more practical goals, such as understanding how the cortex regulates the nucleus accumbens in order to help understand disorders such as substance use. Of course, while that hope led to many discoveries, translating even those simpler goals into treatments proved elusive for my entire career. Nonetheless, hope springs eternal. I believe in the human capacity to discover and create, and I am grateful to have played a small role in helping us eventually achieve some of my earlier aspirations.

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

As implied in the previous answer, my research goals and discoveries became more reductionist over time due to a need to find concrete answers to questions, believing that this could lead to interventions in psychiatric disorders. On this trajectory, I have gone in two general directions, improving preclinical behavioral models of substance use disorder and understanding how the neuropil in which synapses are embedded is essential in curating synaptic activity. In the former, we have explored algorithms for nonlinear modeling of multiple addiction-like behaviors in outbred rats to mimic humans' genetic variability more accurately. By taking multiple traits together and clustering them into resilient and vulnerable subpopulations, we are isolating genetic and transcriptomic traits that may contribute to substance use disorders (SUDs) in humans. For the latter, we are in the vanguard of understanding the 'tetrapartite synapse' – examining how astroglia and extracellular matrix influence synaptic connections between neurons, particularly in pathways from the cortex to nucleus accumbens that regulate reward and addiction-like behaviors. By including key cellular components of the neuropil that in how addictive drugs induce synaptic plasticity, we have encountered new potential molecular mechanisms that in rodents can countermand cue-induced drug seeking.

Early on we focused on a discovery that dysregulation of the astroglial cystine/glutamate exchanger was produced by cocaine use and that restoring it with N-acetylcysteine reduced cue seeking. This was moved into clinical trials with success in reducing cue-craving and in some studies reducing drug use, but it was ineffective in a broad population of significantly reducing relapse except in certain subpopulations, such as already abstinent cocaine users and adolescent cannabis users. The apparent positive effects in subpopulations was an impetus for exploring novel ways to identify subpopulations of rodents using heroin (as mentioned above). Also, this discovery in a possible role for an astroglial protein in regulating drug-relapse induced synaptic plasticity led to two decades of research into how both astroglia and the extracellular matrix regulate both natural reward and drug-induced plasticity in the nucleus accumbens (as also mentioned above).

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

The most critical habit is the ability to focus for hours on end on experimentation and writing. The most important value is that scientific research is a personal art form, akin to painting or any other endeavor where the thrill of discovery and exploration energizes you. With this in mind, in pursuing a career as an experimentalist, I found the hierarchy within science was largely irrelevant to discovery; rather, it was more important to be embedded in a team of colleagues from technicians to students to Principal Investigators (PIs) who have varied perspectives that could shape our research. Of course, the community of science is relevant for funding research, obtaining notoriety in the field, and finding great colleagues and friends.

**At Genomic Press, we prioritize fostering research endeavors 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 deeply stirs your passions?**

First, I was often so wrapped up in conducting competitive research and publishing that only in the last 15 years or so did I come to fully appreciate how grateful I am for the opportunities I was afforded, primarily by taxpayers who are incredibly generous in funding most of my research. The non-science taxpayers need to be admired for their generosity and belief in the positive force scientific discovery brings to civilization. They should be brought into the discussion of science as essential partners. More to the point of the question. Being raised in an upper-middle-class family but attending a public school system that was socio-economically diverse gave me a combination of early exposure to science as well as an appreciation for the role that people with different backgrounds play in advancing human civilization. I applaud the efforts by most of the scientific community to broaden our workforce to include people from all types of backgrounds.

**What do you most enjoy in your capacity as an academic or research leader?**

I have always enjoyed the sense of optimism and excitement of making discoveries in the lab the most. This is amplified by working with my labmates on the same discoveries. As a department chair, this was further amplified by having the resources to play a small role in helping young faculty build their research careers.

**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?**

I spend my leisure exploring the world around me. This takes many forms, from walking in the woods to flying around the world and experiencing cultures and ecosystems that are new to me.

**Part 2: Peter W. Kalivas – Selected questions from the Proust Questionnaire<sup>1</sup>****What is your idea of perfect happiness?**

I am not a big fan of perfection, which I see as a false goal. That said, happiness comes in many forms and really amounts to a general state of optimism, relationships and personal exploration. Family and friends are key facilitators of this state of mind for me.

**What is your greatest fear?**

It is cliché, but I believe that "the only thing we have to fear is fear itself" (Franklin D. Roosevelt's First Inaugural Address, 1933). More specifically, in my lifetime, I have watched fear sap energy from things as varied as the space program to social cohesion. I fear that a political culture using fear

<sup>1</sup>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.



**Figure 2.** Scientific discovery, like life, is a personal art form. Have fun!

as a means to power is detrimental to the scientific and cultural development of our civilization to culturally and scientifically evolve in response to an ever-changing world.

**Which living person do you most admire?**

The more I can share and empathize with another person, the more I admire them. To follow this to its logical conclusion, I would say my wife, Sue King who spent her career as a social worker with children.

**What is your greatest extravagance?**

Indulging my passion for travel by flying.

**What are you most proud of?**

It is prosaic but true to say: my children. This is followed by how well most of the people passing through my lab and department have done for themselves both in their career and personal lives.

**What is your greatest regret?**

I regret not living to be 500 years old, so I would have time to experience different walks of life.

**What is the quality you most admire in people?**

Kindness and trust, which are the antithesis of fear.

**What is the trait you most dislike in people?**

Materialism as a substitute for personal growth.

**What do you consider the most overrated virtue?**

Believing in absolute truth, which distorts understanding the ever-changing reality we live with.

**What is your favorite occupation (or activity)?**

Experiencing new things.

**Where would you most like to live?**

Southern California, with 10% as many people.

<sup>2</sup>“Fortune favors the brave” traces back to ancient Rome, first appearing in Virgil’s Aeneid as “audentes Fortuna iuvat” (29-19 BCE) and in Terence’s Phormio (161 BCE) as “Fortes fortuna adiuvat.” The saying spread across Europe over centuries and lives on today as a motto for military units like the U.S. 3<sup>rd</sup> Marine Regiment. While often credited to Pliny the Elder, scholars cannot confirm he actually coined the famous version we use today – it seems to have evolved naturally from these earlier Roman sources over time.

**What is your most treasured possession?**

My physical and mental health.

**When and where were you happiest? And why were so happy then?**

It is tough to rank-order something like happiness. As I said above, happiness is a state of mind not necessarily linked to a specific event. It is best experienced and shared with others but arises internally sometimes when least expected. It is easier to say in concrete terms what makes me unhappy.

**What is your current state of mind?**

Relatively at peace, trying to answer questions that go beyond words.

**What is your most marked characteristic?**

I like to think it is tolerance, that comes from trying to accept the world as it is, not necessarily how I think it should be. This came in handy as a scientist whose hypotheses were often proven only partly correct or wrong upon further experimentation.

**Among your talents, which one(s) give(s) you a competitive edge?**

Intense focus of attention and generally not taking things personally.

**What do you consider your greatest achievement?**

I will answer this in terms of my career. I hope the people who passed through my lab learned as much from me as I did from them. When I step aside, they will be the ones left to explore and make important, novel discoveries.

**If you could change one thing about yourself, what would it be?**

To have been less afraid of what others think of me, especially when I was younger. It created a lot of unnecessary anxiety and got in my way, especially during public speaking. I self-medicated with beta blockers to treat public speaking anxiety for the first 10-15 years of my career.

**What do you most value in your friends?**

Kindness and an ability to surprise.

**Who are your favorite writers?**

Richard Powers for his descriptions of biological ecosystems that put words to things I experienced but had no words. I also enjoyed Ayn Rand, both for the empowering portrayal of what ambitious, committed people can accomplish, but also for revealing that ambition at the expense of others is an important guardrail to be aware of in building a successful career.

**Who are your heroes of fiction?**

Reading fiction for me until now has been mostly a way to relax and escape, so I never really found a hero. That said, a person (rather mutant) that comes to mind is Charles Francis Xavier, better known as Professor X, has been guiding the X-Men since his first appearance in Marvel Comics’ The X-Men #1 in September 1963. The brainchild of Stan Lee and Jack Kirby, Professor X serves humanity with intelligence and humility, not a bad role model.

**Who are your heroes in real life?**

I admire most people who have had a large personal career and, in later life, give back out of gratitude for what they have received. Jimmy Carter comes to mind.

**What aphorism or motto best encapsulates your life philosophy?**

Fortune favors the brave.<sup>2</sup>

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