Brain Medicine

INNOVATORS & IDEAS: RESEARCH LEADER

Carlos A. Zarate, Jr.: Using clinical translational neuroscience to develop the next generation of antidepressant treatments that act more rapidly and effectively

Carlos A. Zarate, Jr., MD, spearheads transformative research in psychiatry and neuroscience. As a National Institutes of Health (NIH) Distinguished Investigator, he leads the Experimental Therapeutics and Pathophysiology Branch and the Section on the Neurobiology and Treatment of Mood Disorders at the National Institute of Mental Health (NIMH). His additional role as Clinical Professor of Psychiatry and Behavioral Sciences at George Washington University underscores his commitment to research and education. Dr. Zarate's pioneering work focuses on decoding the pathophysiology of treatment-resistant mood disorders and suicide while developing novel therapeutics that are reshaping approaches to patient care. His research integrates cutting-edge techniques from neuropsychopharmacology, electrophysiology, neuropsychology, neuroimaging, and genomics to forge new pathways in treating mood disorders. Perhaps most notably, Dr. Zarate's team has been instrumental in demonstrating that ketamine, an NMDA receptor antagonist, can produce rapid and long-lasting antidepressant and anti-suicidal effects. This discovery has catalyzed a paradigm shift in psychiatry, proving that antidepressant response within hours, not weeks, is achievable. Dr. Zarate's innovative approach extends beyond the lab. He employs a bi-directional translational strategy, seamlessly integrating clinical, behavioral, and imaging technologies with basic science collaborations. This holistic method has led to numerous breakthroughs in mood disorders research, addressing critical issues such as the speed and efficacy of current treatments. His exceptional contributions to the field have earned him numerous accolades, including election to the National Academy of Medicine in 2020. These honors recognize his research excellence, his innovative spirit, and his dedication to mentoring the next generation of scientists. We are privileged to feature Dr. Zarate in this Genomic Press interview. His insights promise to offer our readers a glimpse into the cutting edge of psychiatry and the tangible hope his work brings to millions suffering from mood disorders.

Part 1: Carlos A. Zarate, Jr. – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?
Oddly enough, my professional journey began with tennis. During high school in Cordoba, Argentina, I gave tennis lessons to the chief of cardiovascular surgery at a private hospital. In return, he allowed me to observe cardiac surgeries and neurosurgeries. I spent all my summers in high school doing that and fell in love with neurosurgery, which led me to get interested in the brain. I went to medical school at the Catholic University of Cordoba, and after moving to the USA and completing the clinical part of my foreign medical exam, I was fortunate enough to be offered a psychiatry residency at the Massachusetts Mental Health Center/Brockton Veterans Administration Medical Center. There, I was inspired by some of

Figure 1. Carlos A. Zarate Jr, MD, National Institute of Mental Health, National Institutes of Health, USA.

the "legends of neurobiology and psychopharmacology" at the time, including Drs. Ming Tsuang, Robert McCarley, Alan Schatzberg, Alan Green, Carl Salzman, and Joe Schildkraut. I later solidified my interest in clinical psychopharmacology research under the influence and mentorship of Drs. Mauricio Tohen, Anthony Rothschild, Bruce Cohen, Jonathan Cole, and Ross Baldessarini at McLean Hospital.

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?
At McLean Hospital, I was allowed to create and develop the Experimental Psychopharmacology Clinic with Dr. Mauricio Tohen. During my fellowship, it became clear that despite the effective medications and psychotherapies at the time, many patients were unable to achieve complete
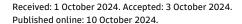
Figure 2. Dr. Carlos Zarate catching up on work while soaking in the views of the Sierras de Córdoba, Argentina. From his terrace vantage point, he overlooks Lake San Roque, its waters stretching out amidst the rolling hills. The Sierras, with their mix of lush and rugged terrain, offer a striking change of scenery from the clinical environment of NIH. This quiet corner of central Argentina, dotted with small towns and resorts, gives Dr. Zarate a moment of respite. Here, surrounded by nature, he finds space for reflection – a valuable asset for his innovative work in psychiatric research.

remission or recovery. For that reason, Dr. Tohen and I decided to pursue novel therapies with the goal of obtaining treatments that were significantly more efficacious than existing ones at the time. However, I could see that we were only making minor incremental progress with some of the new medicines we were testing in the clinic. I realized that I needed to pursue more rigorous neurobiology and neuropsychopharmacology training and research to approach the problem from that perspective. I was recruited to the National Institute of Mental Health (NIMH) in 2001, where I developed a neurobiology and experimental therapeutics program focused on tackling the challenge of developing novel and improved treatments for mood disorders, a program I continue to lead.

Please share with us what initially piqued your interest in your favorite research or professional focus area
From the beginning, the driving force underlying all my research efforts has been that most currently available antidepressant treatments require weeks to months to achieve their full effects, and many patients do not respond to them at all. When I began my clinical career, it was immediately apparent that this lack of rapid-acting, safe, and effective therapeutics was a major public health concern that prolonged suffering and led to adverse outcomes for our patients. During my fellowship at McLean Hospital, I was seeing literally hundreds of people with severe bipolar disorder, psychosis, schizophrenia, and schizoaffective disorder. While we could help patients with standard therapeutics, their quality of life and function was not excellent. The realization that we needed to come up with better treatments laid the groundwork for one of my most significant accomplishments: changing the way we study patients with severe mental disorders (both those with treatment-resistant depression and suicide ideation). Prior to the creation of our Branch at the NIMH in mid-2000, very little research had been conducted into experimental therapeutics and neurobiology for the seriously mentally ill for several reasons. These include the ethics of studying patients with severe depression in a drug-free state, the feasibility of studying biomarkers in a drug-free state (in order to better understand the neurobiology of disease and effects of the medicine under investigation), and the logistics of conducting proof-of-concept studies with experimental drugs in such patients. Envisioning, developing, instituting, and successfully and safely conducting such research has been the driving force of my career.

What impact do you hope to achieve in your field by focusing on specific research topics?
The ultimate goal of all my research efforts is to develop better and safer treatments for our patients and alleviate the suffering of millions of individuals worldwide with mood disorders. Globally, my work with ketamine has already had a clear, transformative impact on mental health, and I anticipate that my continued research into the mechanisms of ketamine and its metabolites will significantly increase our knowledge of the neurobiological targets involved in rapid antidepressant effects, the biomarkers that predict clinical improvement, and the neurobiology underlying the therapeutic response. To date, my paradigm-shifting research—especially with regard to the rapid antidepressant effects of ketamine—has already raised the bar for developing the next generation of faster-acting and more effective antidepressants.

Please tell us more about your current scholarly focal points within your chosen field of science
My lab conducts cutting-edge, high-risk, high-impact research in mood disorders and suicidal behaviors. Our proof-of-concept studies use novel compounds and neuroimaging, electrophysiology, and other central and peripheral biomarkers, and we collaborate across many disciplines to identify potentially relevant drug targets, biosignatures of treatment response, and treatments for mood disorders (major depressive disorder and bipolar disorder) and suicidal behavior. In the short term, we have recently begun a Phase 2 trial of the ketamine metabolite (2R,6R)-HNK, which is not an anesthetic agent, has no dissociative side effects, and no misuse potential.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
First, service. Those who know me know that service has always been an essential part of my personal and professional life, and I often think of my work to develop novel treatments for mood disorders as a public service. Second, gratitude. It is impossible not to reflect on my career without gratitude for the many opportunities I have been granted. Third, diversity. My overarching philosophy is that diversity is good for science. The term "diversity" is often used or misused, but I consider it to mean diversity of thought, scientific background, or opinion. We have made progress in this area, but more progress is needed.

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?
It has become increasingly clear that collaboration is the secret to transformational science. As an example, the past few decades have seen concerted efforts by "Team Science"—universities, Government, private foundations, industry, and advocacy groups—to find and develop better treatments for patients with mood disorders. Multiple technologies, including genetics, proteomics, transcriptomics, optical genetics, induced pluripotent stem cells, and neuroimaging (to name a few), have been used to explore the pathophysiology of these disorders. I believe that in our interconnected world, cross-disciplinary and cross-organizational collaborations will be needed to advance the field significantly.

What do you most enjoy in your capacity as an academic or research leader?
The work is essential, but it is also fun to mentor trainees. I really enjoy seeing them progress through their careers from training to independence. The NIMH intramural research program allows for high-risk, innovative research that would be very hard to do outside of the intramural research program. It is both unique and rewarding and permits us to train and develop the next generation of investigators. Ultimately, they are the ones who will pave the way to full recovery or "cures" for our patients.

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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 am a big fan of sci-fi films, love to read, and enjoy spending time with my family.

Part 2: Carlos A. Zarate, Jr. – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Conceptually, I do not pursue perfect happiness. Instead, I view myself as continuously blessed with all the opportunities that have come my way. This allows me to continue to serve and enjoy what I have.

What is your greatest fear?
Not being able to serve or contribute in a meaningful way, not being able to help those who suffer.

Which living person do you most admire?
My wife, Silvina. She has an immensely rich life of faith, spirituality, and service. She keeps me grounded and helps me become a better person.

What is your greatest extravagance?
Everything that I do not need is an extravagance. I do not need material things; rather, I focus on the pleasure I get from seeing people smile, laugh, and do well.

What are you most proud of?
This question is difficult to answer. I tend not to feel pride, preferring to focus on my enormous sense of gratitude.

What is your greatest regret?
Not being able to do more for others.

What is the quality you most admire in people?
The quality I enjoy most in people is their uniqueness. Everyone has their own lives, career goals, passions, and ways of thinking—their creativity. I enjoy getting to know people and working together to tackle important problems.

What is the trait you most dislike in people?
I honestly try not to say or think that "I don't like" or "hate" something. Instead, I like to think that there is something worth liking in everyone.

What do you consider the most overrated virtue?
Our virtues are special graces given to us; they are present in each of us to different degrees and make us unique individuals.

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[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.

What is your favorite occupation (or activity)?
There are many: reading, having conversations with and interacting with others, spending time with my family, eating asados, enjoying the beautiful views in las Sierras de Cordoba, Argentina (Figure 2), etc.

Where would you most like to live?
Exactly where I live now.

What is your most treasured possession?
I do not have a "treasured possession." My family—including my wife and children—and my faith are the most important things in my life. They are not my possessions but what is most meaningful to me.

When and where were you happiest? And why were so happy then?
In general, I always feel content and at peace.

What is your current state of mind?
Calm and at peace.

What is your most marked characteristic?
I usually leave it to others to describe what they see. Perhaps it is my ability to stay calm and always make it clear to others that I am available to help.

Among your talents, which one(s) give(s) you a competitive edge?
Being able to see solutions to problems that others may not see and setting up systems to get the job done

What do you consider your greatest achievement?
Setting up the necessary systems and infrastructure (e.g., research methods and next-generation researchers) to investigate current and future problems in psychiatric research.

If you could change one thing about yourself, what would it be?
This is a work in progress. I like to think we continue to grow and change over time for the better.

What do you most value in your friends?
Loyalty, as well as being open to letting me know when they need help.

Who are your favorite writers?
The Bible. Edgar Allen Poe, Robert Frost, and many others.

Who are your heroes of fiction?
I enjoy fiction but do not consider those characters my heroes. Rather, I am interested in each character's makeup and how they interact with each other to advance the story, deal with villains, and help those in need.
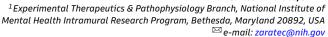
Who are your heroes in real life?
My wife Silvina and children Carolina, Diego, and Sofia – in other words, my family.

What aphorism or motto best encapsulates your life philosophy?
"I'm gonna have to science the shit out of this."
    Mark Watney (played by Matt Damon in *The Martian*).

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