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INNOVATORS & IDEAS: RESEARCH LEADER

Károly Mirnics: Many medications and chemicals might not be as safe for the developing brain as we think they are; this will greatly depend on your genotype, habits, and environmental factors

Brain Medicine July 2025;1(4):10–13; doi: https://doi.org/10.61373/bm024k.0028

Keywords: Gene*medication interactions, sterol biosynthesis, brain development, neurodevelopmental disorders, schizophrenia

Károly Mirnics is Director and Hattie B. Munroe Professor of Psychiatry, Biochemistry & Molecular Biology, Pharmacology & Experimental Neuroscience, Munroe-Meyer Institute for Genetics and Rehabilitation at the University of Nebraska Medical Center (UNMC). Dr. Mirnics earned his medical degree from the University of Novi Sad School of Medicine (in the former war-torn country of Yugoslavia that does not exist anymore) and his Ph.D. from Semmelweis University in Budapest, Hungary. He completed his postdoctoral fellowship at the University of Pittsburgh, where he established his laboratory in 2000. In 2006, his laboratory moved to the Department of Psychiatry at Vanderbilt University in Nashville, TN. In 2010, Dr. Mirnics was named James G. Blakemore Professor of Psychiatry and served as the departmental vice chair for research and the associate Director of the Vanderbilt Kennedy Center for Human Development. In 2016, he joined UNMC, becoming the Director of the Munroe-Meyer Institute for Genetics and Rehabilitation (MMI). With over 1,000 employees and trainees and roots tracing back to 1919, MMI is among the world's most extensive clinical, research, education, and outreach institutes for intellectual and developmental disabilities (IDD). Funded by the National Institutes of Health (NIH), Dr. Mirnics's innovative research uses a variety of genetic, molecular, cell biology, and behavioral tools across multiple disease models; he has authored over 150 scientific publications, which have been cited more than 17,000 times. As a passionate advocate for diversity, access, and inclusion of individuals with intellectual and developmental disabilities, he currently serves on the board of directors of Special Olympic International (SOI). He chairs the SOI Global Medical Advisory Committee that develops strategies to address the health challenges of more than six million athletes across over 200 countries. He led UNMC's effort to build a highly advanced, award-winning, 20,000 m^2 multidisciplinary building that serves individuals with intellectual and developmental disabilities across the lifespan. We are delighted that Dr. Mirnics shares his personal and professional paths with our readers.

Part 1: Károly Mirnics – Life and Career

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

I do not know if there was a pivotal moment; I undoubtedly do not recall one. From childhood, I wanted to know how things worked. I think I always wanted (or was on a path) to be a scientist. I had great science teachers from my earliest education. They instilled in me a love for the unknown and curiosity about how biological systems work.

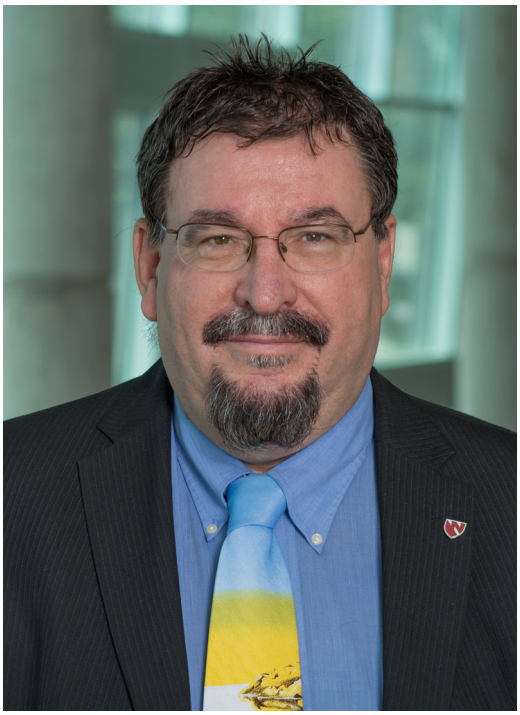

Figure 1. Károly Mirnics, MD, PhD, University of Nebraska Medical Center, USA.

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?

Under the guidance of Pat Levitt and David A. Lewis at the University of Pittsburgh, I learned to be bold and to ask the right questions as a scientist. These mentors also taught me that being bold and being reckless, while on the same continuum, are two very different things. They taught me not to overinterpret my data but to pay attention to all findings that do not make sense, as those might be the most valuable pieces of the puzzle. At Vanderbilt University, I was given an opportunity to get involved in community engagement work and learn management skills. At UNMC, I honed my changemaker and impactful leadership skills. At Special Olympics International, I learned to admire and respect cultures and design systems across various beliefs and customs. Along the way, I had guidance and mentoring from many amazing people, and I am eternally thankful to them. Still, the most pivotal moment in my career was

Received: 7 April 2024. Accepted: 10 April 2024.
Published online: 17 April 2024.

meeting and working for Pat Levitt, who remains my idol in multiple ways. His "superpower" is caring – about people, science, and society, which makes him a terrific role model.

Please share with us what initially piqued your interest in your favorite research or professional focus area.
Cholesterol gets a bad rap in the public and, to a certain degree, in the medical community. Sterol biosynthesis in the developing brain is essential, yet still much of an enigma. The brain contains about 25 percent of the cholesterol of humans, and the synthesis of all this cholesterol is entirely independent of the systemic cholesterol of the body. We cannot live without it, and the sterol biosynthesis pathway is essential for virtually all cellular and molecular processes. This almost incomprehensible complexity fascinates me, and the Janus duality of cholesterol reminds me daily of the inevitable yin-yang aspect of my everyday life and work – well beyond the scientific endeavors we pursue.

What impact do you hope to achieve in your field by focusing on specific research topics?
The neuroscience and medical fields need to understand how vital sterol biosynthesis is for the developing brain and that many commonly used medications can interfere with it, potentially with very deleterious consequences. All medications must be evaluated for their potential to inhibit brain cholesterol biosynthesis, especially in development and in the context of the mother's and child's genotype. I also hope to identify chemical compounds that would regulate brain cholesterol biosynthesis (or counteract inhibition of it) in conditions where this homeostasis is disrupted.

Please tell us more about your current scholarly focal points within your chosen field of science.
Our lab's recent primary focus is sterol biosynthesis and homeostasis in the developing brain. We investigate critical time windows, the effects of medications on this process, and how and when genotype worsens sterol biosynthesis inhibition by chemicals, lifestyle, and medications. Our previous work focused on gene expression patterns in postmortem brains of subjects with schizophrenia, the role of interneuronal classes in regulating behaviors, and genotype*maternal immune activation interactions. We also explored molecular mechanisms of neuroprotection by exercise and physical activity.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
Honesty, hard work, being transparent, not mincing words, and having compassion are critical traits that I learned from my mentors – which I will treasure for the rest of my life.

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?
Our perspective tends to be overly centered on Western civilization. The phrase "Let a hundred flowers blossom," championed by the Chinese intellectual community in 1957 to improve their nation, strikes a chord with me. Embracing cultural variances is crucial; our collective diversity constitutes our collective strength. Unfortunately, the prevalent view remains skewed toward certain cultures and demographics. I am concerned about the widespread notion that groundbreaking ideas and superior scientific contributions are exclusive to top-tier institutions like the Ivy League and their equivalents, leading to overestimating their research outputs. This bias is evident in the grant review process, the selection of studies for leading journals, and the portrayal of scientists in major media channels. However, this perception does not align with reality. Exceptional scientific work is not confined by geography. Take my journey as an illustration: I originated from a nation that no longer exists and earned my qualifications from a lesser-known institution. Nevertheless, I currently lead a globally acclaimed institute specializing in developmental disabilities.

Figure 2. Károly Mirnics with a patient at the Munroe-Meyer Institute playground.

What do you most enjoy in your capacity as an academic or research leader?
I love seeing other people reach their potential and be amazing at what they do. I love the smiles on the athletes' faces at Special Olympics International events. I love knowing that I made this world a little bit better place for someone.

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 enjoy reading a sci-fi book, traveling to new places, fishing or hiking, playing online chess, and talking on the phone with my family.

Part 2: Károly Mirnics – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Depends on the day, my mood or activities, and the circumstances: at work, getting a perfect score on R01 grant or obtaining an extraordinary result in our research study. At a personal level, being on a small fishing boat in Alaska with a big one on my hook, watching the incredible sunsets over the lake with my family, getting overwhelmed by the sound of amazing music at the symphony are all things that give me joy. I find my happy moments whenever I can. I am not picky, and I learned to enjoy the half-full glass.

[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 greatest fear?
This is a tough one. I do not have many fears. Fear inhibits and makes you vulnerable. Fear is not a strategy; you cannot allow it to have power over you; it paralyzes decision-making. My greatest fears are probably related to the health and well-being of my family members.

Which living person do you most admire?
Many different individuals for their particular traits and skills. I will not name them all, as I will leave out many important people in my life from this list. Pat Levitt for his knowledge, passion, dedication to trainees, brain power, and moral/ethical qualities in the scientific community. In public life, I most admire Tim Shriver for his amazing, tireless work in Special Olympics International and his advocacy for civility and dignity. In daily life, my wife, Zeljka Korade, for her unparalleled human qualities, passion for science, hard work, and personality. I admire everyone who cares about their work or activities. Caring is the secret sauce of life and a precondition for doing things well.

What is your greatest extravagance?
I am not sure. You will have to ask my wife and friends. Wearing colorful ties, buying fishing lures that I will probably never use, and owning various hats are the furthest I go in this arena.

What are you most proud of?
Being myself. Speaking truth to power. Being creative and accomplishing almost impossible things even when they are incredibly challenging. Creating frameworks for other people to succeed. Being honest.

What is your greatest regret?
I do not look back with regrets. It makes no sense for me to play the *"what if"* game. I am happy with my life; I have been fortunate and blessed with a job I love, financial security, health, and an adorable family. I regret gaining too much weight, getting hooked on nicotine, occasionally not being kinder to others, and other similar things.

What is the quality you most admire in people?
Being grounded, honest, and comfortable with who they are. I sincerely believe that only caring, friendly people can be happy.

What is the trait you most dislike in people?
Traits, actually. Greed, self-centeredness, selfishness, rigidity, and forcing our beliefs on others are the banes of our society.

What do you consider the most overrated virtue?
It has to be intelligence. I have met many incredible people with intellectual and developmental disabilities who are remarkable human beings. In contrast, I also met crooks whose intelligence was off the scale. This makes you think about what we value *vs.* what we should value in society.

What is your favorite occupation (or activity)?
Traveling to new places, fishing, hiking, kayaking, playing chess online, having family get-togethers over videoconferencing, and having a scotch while watching the sunset over the lake.

Where would you most like to live?
Alaska or Iceland in the summer, Sint Maarten/Saint Martin or Dominica in the winter. I am also very content in Nebraska, as I love the Midwest. The people here are lovely and genuine. It is like where I was born – the big sky, incredible sunsets, swaying crops in the wind, big rivers with incredible wildlife: what is not to like?

What is your most treasured possession?
My family, my health, my memories of our family travels.

When and where were you happiest? And why were you so happy then?
I have had many unforgettable moments in life. However, I cannot think of one that would stand out as the "one" happiest moment—my happiest moments included the ones you would expect – coming to the US, getting married 30 years ago, the birth of our two children, getting a tenure-track job, finishing my first marathon, obtaining my first grant as a PI, signing the purchase documents on our first home. One period may stand out. Zeljka and I were trainees at the University of Pittsburgh, with very meager resources (long story), but we had each other and a city and area full of wonders to explore.

What is your current state of mind?
I am worried. For the state of our country, the poisoned rhetoric, the relativity of truth, and the extreme polarization that has become the norm. I am very much a centrist, and there is no place for people like me in our current political landscape. However, this question has a variety of answers. Depending on my activities, focus, and surroundings, my mind will change in the next five minutes.

What is your most marked characteristic?
Most say speaking my mind (perhaps too much!) and wearing my emotions on my sleeve. On the other hand, vision, fairness, and integrity are my best qualities. One of my directors always describes me as a teddy bear at heart with the appearance and manners of a grizzly bear.

Among your talents, which one(s) give(s) you a competitive edge?
My above-listed characteristics, coupled with hard work.

What do you consider your greatest achievement?
Designing and building the world's most advanced building for diagnosis and treatment of intellectual and developmental disabilities[2], changing the culture of MMI to be more collaborative, and changing the hearts and minds of our providers to focus on excellence throughout all our activities – with our patients and their families being the focal point.

If you could change one thing about yourself, what would it be?
I want to become a better listener, less deeply invested in my own ideas, and less impatient. I always favor action over inaction, and it would be nice to have a more balanced mindset. I have come a long way but am still a work in progress.

What do you most value in your friends?
Being genuine. Being who they are and not pretending and posturing.

Who are your favorite writers?
Ray Bradbury, David Niven, Isaac Asimov, Orson Scott Card, James P. Owen, Stanisław Lem, Arthur C. Clarke, Partick Rothfuss, Ursula K. Le Guin, Roger Zelazny, George R. R. Martin, Brandon Sanderson, Aldous Huxley, Neil Gaiman, Dan Simmons and many other sci-fi and fantasy writers.

Who are your heroes of fiction?
They share the common characteristic of not being purely good or purely evil. They are human, complex characters. Examples include, but are not limited to, Takeshi Kovacs (Altered Carbon), Kvothe (Name of the Wind), Martin Silenus (Hyperion), and Louis Gridley Wu (Ringworld).

Who are your heroes in real life?
All people who are not in it for money, fame, or personal gain. The unnamed ones that history books will never remember. Single mothers working three jobs, the late Dr. Gorog Istvan from Orebić, Croatia, who worked 18-hour days as the only physician in the diameter of 60 miles, my science teachers and university professors, daycare workers, people who speak up for justice and humanity regardless of grave personal consequences on their lives and freedom, the ones who feed people experiencing poverty yet they have little to feed themselves, and so on. Forgotten inventors who changed the course of human history with fire, wheel, and metal, astronomers of ancient cultures. The list is endless.

[2]For further details on the Munroe-Meyer Institute, see https://vimeo.com/560450619/a1fb34aa0d.

https://doi.org/10.61373/bm024k.0028

What aphorism or motto best encapsulates your life philosophy?
Immanuel Kant's quote guided my life since I read *"Critique of Practical Reason"* at age of 17: *"... the starry heavens above me and the moral law within me."* For me, this always meant that human potential is unlimited and that we must dream big and think the unthinkable. The limit is not what we can achieve. Rather the limits should come from the ethical boundaries of a universal moral code contained within all of us. We have to listen to it and tune out our desires and wants.

My leadership philosophy is best summed up in the book Cowboy Ethics by James P. Owen. In particular, the following paragraph strongly resonates with me: *"The fundamental problem is that we have confused rules with principles. Rules can always be bent, but principles cannot. So, while bureaucratic rules may reinforce the ways we ought to behave, they are no substitute for personal principles."*

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