Genomic Press
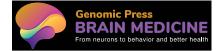**BRAIN MEDICINE**
From neurons to behavior and better health

🔓 **OPEN**

INNOVATORS & IDEAS: RESEARCH LEADER

Etienne Sibille: Investigating the cellular and molecular bases of depression and aging for innovative therapeutics

Etienne Sibille, a pioneering figure in neuropsychiatric research, has yet to follow conventional paths. From his early days as a photojournalist editor in New York to becoming one of neuroscience's most innovative voices, his journey reflects the same creative thinking that drives his groundbreaking research at the University of Toronto. As a Professor of Psychiatry, Pharmacology & Toxicology, he brings a fresh perspective to understanding how our brains age and why we get depressed. At the Center for Addiction and Mental Health (CAMH), where he directs the Neurobiology of Depression and Aging research program, his team is turning fascinating discoveries about brain chemistry into potential new treatments. Building on his influential work at Columbia University and the University of Pittsburgh, Sibille has challenged traditional views of brain disorders, particularly through his insights into the GABAergic system and aging. While serving as CAMH's Campbell Chair (2014–2024) and Deputy Director of the Campbell Institute (2017–2020), he has pushed the boundaries between basic research and real-world treatments, recently diving into biopharma development to help bridge this gap. In this Genomic Press Interview, he shares the winding road that led him from behind a camera lens to the forefront of psychiatric research, offering a candid look at what drives his passion for unraveling the brain's mysteries.

Part 1: Etienne Sibille – 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 grew up in France and attended medical school, but it was not for me. I was too restless and moved to New York to pursue a career in photography and journalism. The biotech boom in the 1990s created a lot of hope and enthusiasm that the biological sciences could finally tackle some of the problematic brain-related challenges with a huge potential impact on individuals' quality of life and society at large. Since I have always had affinities and capabilities for the life sciences, I jumped when an opportunity to go back to science presented itself. I did a PhD in Pharmacology at Cornell with Miklos Toth, a postdoc at Columbia with René Hen, and then trained in human postmortem studies with Victoria Arango before setting up my lab at Columbia, then at the University of Pittsburgh. My career changes and moves have never been planned and have resulted from opportunities that presented themselves through scientific networks. In 2014, I moved to CAMH and the University of Toronto to set up a program on the molecular bases of depression and aging, with a strong focus on translation and drug development for brain disorders.

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?
My more relevant leadership roles involve guiding multidisciplinary research groups and focusing them on a particular research question. I have

Figure 1. Etienne Sibille, PhD, University of Toronto and The Centre for Addiction and Mental Health, Canada

some aptitude for seeing big pictures, but I also realize that it takes a village to bring them to fruition. These goals and visions drove me to leadership roles as necessary means but hopefully also as key stimulating factors in generating group enthusiasm towards a shared goal.

Please share with us what initially piqued your interest in your favorite research or professional focus area
I have always been fascinated by the fact that small molecules can profoundly affect brain functions, including aspects that make us who we are (e.g., emotions, creativity, drive). Rather quickly, it became apparent to me that I would dedicate my time and energy to understanding underlying mechanisms and harness them toward the goal of reducing the burden of mental health conditions. However, after training in rodent genetics, I grew frustrated by the need for new ideas and directions for novel neuropsychiatric interventions. So, when the opportunity presented itself, I moved to human postmortem studies to generate new leads and ideas based on the primary pathologies of brain disorders. Results from early omics studies we performed in the human brain were so stunning (e.g., effects of age and sex, reduced neurotrophic effects, altered GABAergic

function) in both control and affected individuals that they have led my research program for the following (now) decades.

What impact do you hope to achieve in your field by focusing on specific research topics?
My hope for impact—in other words, what wakes me up early every morning and gets me going—is that I will have enough time for our understanding of novel pathophysiological mechanisms to translate into tangible changes in someone's life. The next question addresses my hope for specific research topics.

Please tell us more about your current scholarly focal points within your chosen field of science
Two main themes emerged from our early human postmortem studies: disturbances in aspects of the GABAergic system and the interaction of age and brain disorders. These two themes have largely dominated my research program since. For the GABAergic system, we have now gone from correlational studies in human brains in depression and aging to causal links in rodent systems, identification of novel targets (subunit-specific GABA-A receptors), and development of novel therapeutics to address the unmet clinical needs of cognitive deficits in depression and age-related disorders. The fact that we will soon have the opportunity to test it in clinical trials is a dream for a basic scientist. For the second theme of age-by-disease interaction, I hope that some of the weak biological links we have identified in postmortem studies will similarly translate into testable hypotheses in clinical trials to support brain health and delay/prevent aspects of age-related disorders.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
I often tell trainees that science is exciting but tedious, requiring tenacity and a high tolerance for failure. So early on, I developed robust work scheduling ethics: I never stopped. This avoids overcoming the high energy barrier to get started (on grants, papers, analyses, etc). I still take time off, but my mind never gets off projects. It works for me, and I enjoy it, but it may only work for some.

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?
A single culture can have dominant and restricting effects. So, I have strived over the years to create a research environment that is multicultural, rich in various perspectives, and not dominated by a single culture. I believe this supports better mental health and creates a more fertile ground for creativity.

What do you most enjoy in your capacity as an academic or research leader?
I love to see the trajectories of trainees at all levels. It is a real pleasure for me to see people develop their sense of self and grow into their careers over time.

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?
Outside of work, I spend a lot of time outside, working on projects on my property, and taking care of animals (dogs, horses). Reading is also important. My reading list is quite eclectic, including fiction, mystery, historical novels and science, either in English or French.

Figure 2. "Rock the World." Professor Etienne Sibille demonstrates his enthusiasm for science and music against a tie-dye backdrop. While his childhood dream of playing guitar like *The Who*'s Pete Townshend may have evolved into air guitar performances, Dr. Sibille channels that same rock star energy into his groundbreaking neuroscience research. The playful image captures his philosophy that revolutionary scientific discoveries, like great music, can genuinely "rock the world."

Part 2: Etienne Sibille – Selected questions from the Proust Questionnaire[1]
What is your idea of perfect happiness?
I am at home in the country with my family (and my dogs and horses) and traveling to new places regularly.

What is your greatest fear?
None that I can think of. I prefer to focus on the present.

Which living person do you most admire?
I do not think in these terms, but I have had various mentors who have significantly shaped my scientific thinking over the years, including Miklos Toth, René Hen, Catherine Belzung, David Lewis, Victoria Arango, and Ron Duman. From my previous career in photography, I also have great respect

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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.

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and appreciation for the works of socially aware photographers, such as Sebastião Salgado and the Magnum Photos team.

What is your greatest extravagance?
I am not sure. I would probably try to forget about it.

What are you most proud of?
I am not sure either. I am proud of the team's many accomplishments and the fact that we are in the process of translating basic findings into potential clinical reality. This is being accomplished through Damona, a biopharma company I have co-founded with CAMH.

What is your greatest regret?
The same here. I do not really think in terms of personal life goals to achieve, and I tend to focus on the present. There were some childhood dreams. As a kid, I wanted to play guitar like Pete Townsend from The Who. But I have no sense of music, and all I can do is play air guitar on beach toys (see Figure 2).

What is the quality you most admire in people?
Integrity, vision, and persistence.

What is the trait you most dislike in people?
Arrogance and blind ambition.

What do you consider the most overrated virtue?
Modesty. In science, it is hard to be too modest and succeed.

What is your favorite occupation (or activity)?
Being in the present, doing what I am doing.

Where would you most like to live?
After living in Europe and the US, I am delighted to have landed in Canada. Frequent trips to Paris and Europe provide the perfect balance.

What is your most treasured possession?
I enjoy possessions but do not treasure them.

When and where were you happiest? And why were so happy then?
At work, I tend to have data-dependent mood states, so they vary from day to day (and over grant cycles...). In my career, I have truly enjoyed all the places I have been fortunate to work at (Cornell, Columbia, Pittsburgh, and now Toronto).

What is your current state of mind?
I am hopeful for the future of neuropsychiatry, merging with neuroscience and evolving into precision medicine.

What is your most marked characteristic?
I easily see the big picture and quickly analyze it. I believe that I have also been a good mentor over the years.

Among your talents, which one(s) give(s) you a competitive edge?
Seeing what other people do not see.

What do you consider your greatest achievement?
Having sustained a rich scientific and mostly stable scientific team and environment over the years.

If you could change one thing about yourself, what would it be?
Not sure. I do not spend too much time thinking about how to change myself.

What do you most value in your friends?
The safe space they can provide

Who are your favorite writers?
It varies. Recently, I have tremendously enjoyed reading the Louise Penny series on Inspecteur-chef Armand Gamache.

Who are your heroes of fiction?
I am still trying to decide.

Who are your heroes in real life?
I do not think along these lines, but I have greatly admired greater-than-life personalities like Nelson Mandela.

What aphorism or motto best encapsulates your life philosophy?
Work on topics that excite you, balance your private life, eliminate useless activities, and empower people around you in their private and professional lives.

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