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INNOVATORS & IDEAS: RISING STAR

Hamilton Oh: A journey studying the science of humanity

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Dr. Hamilton Se-Hwee Oh is pioneering groundbreaking research at the intersection of neuroscience, immunology, and aging biology at Mount Sinai's prestigious Brain-Body Institute and Ronald M. Loeb Center for Alzheimer's Disease, where he decodes the complex bidirectional communication between the brain and peripheral organs that drives depression, aging, and neurodegeneration. Working under the renowned mentorship of Drs. Scott Russo and Alison Goate, Dr. Oh bridges neuroscience, immunology, and computational biology to decode how psychological stress accelerates organ aging and how peripheral molecular signals rewire neural circuits affecting mood, cognition, and long-term health. His groundbreaking Stanford PhD research in the Wyss-Coray laboratory yielded three first-authored high-impact *publications in Nature* and *Nature Medicine*, including revolutionary discoveries that demonstrated human organs age at differential rates with profound implications for disease susceptibility. Additionally, he identified cerebrospinal fluid synaptic biomarkers that predict Alzheimer's dementia onset years before clinical manifestation. By integrating large-scale human proteomics, single-cell transcriptomics, and mechanistic animal models, Dr. Oh pioneers precision medicine approaches targeting root causes of depression, chronic pain, and age-related neurodegenerative diseases. His innovative research examines how immune cells and metabolic organs amplify or dampen mood symptoms, utilizing cutting-edge metabolomic and proteomic profiling to identify peripheral proteins and metabolites that track depressive behavior. Currently investigating the molecular fingerprints of interventions such as exercise and ketamine, Dr. Oh's multidisciplinary approach positions him at the forefront of developing next-generation therapies. His work exemplifies how young scientists can leverage big data and systems biology to transform our understanding of brain-body interactions, offering hope for millions suffering from neuropsychiatric and neurodegenerative disorders worldwide.

Figure 1. Hamilton Se-Hwee Oh, PhD, Icahn School of Medicine at Mount Sinai, USA.

Part 1: Hamilton Oh – Life and Career

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

I was born in North Carolina, USA. I now live in New York City, New York, USA.

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 Connecticut as an active kid who loved playing outdoors, whether in the water, snow, or piles of autumn leaves, depending on the season. At school, my favorite subject was math, and at home, I spent hours building with Legos and playing video games. My interest in biology began to take shape in high school, when I became more reflective about my own life and the lives of those around me, especially after learning the concept of *sonder* in my humanities class: the realization that every person lives a life as vivid and complex as our own. It amazed me that this rich, emotional, subjective experience could arise from the coordinated activity of trillions of cells. What ultimately drove me to study biology in college, though, was personal experience. I was diagnosed with a rare chronic kidney disease (which, fortunately, remains stable today), and I watched my best friend develop a persistent, unexplained abdominal pain that continues to affect his life. I hoped that by studying the intricate inner workings of life, I might one day contribute to curing the kinds of conditions that cause such deep and often invisible suffering.

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

As an undergraduate at the University of California, Los Angeles (UCLA), I was drawn to the promise of stem cell research and its potential to revolutionize treatments for degenerative diseases. Around the same time, I kept encountering references to "inflammation" across a wide range of diseases, from cancer to heart disease, which led me to think that studying the immune system's stem cells, hematopoietic stem cells, could be a promising direction. This curiosity brought me to Hanna Mikkola's lab,

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where I investigated how specific transcription factors regulate the development of hematopoietic stem cells during embryogenesis in mice. While I found the study of intracellular mechanisms governing stem cell identity fascinating, I became increasingly intrigued by the role of the surrounding microenvironment, the stem cell niche, and how external cues from neighboring cells influence stem cell development and function.

This interest led me to pursue a PhD in Stem Cell Biology and Regenerative Medicine at Stanford University, where I initially set out to study how the adult bone marrow niche regulates hematopoietic stem cells during immune system regeneration. But as often happens in science, my interests evolved. During a rotation in Tony Wyss-Coray's lab, I became captivated by the interplay between the immune system and the brain in the context of aging and Alzheimer's disease. I began by culturing neurons with T cells to explore their interactions and later analyzed single-cell transcriptomes from immune cells in the cerebrospinal fluid of Alzheimer's patients.

I was excited by the opportunity to study human disease directly, especially at a time when high-throughput molecular profiling technologies were offering unprecedented resolution into human biology. I also rediscovered my fascination with the brain, the organ central to emotion, consciousness, and self, concepts that had first sparked my interest in biology during high school. At the same time, I realized that aging itself is a powerful upstream driver of many chronic diseases and that understanding it could offer broad insights into disease prevention and healthy longevity.

I ultimately joined the Wyss-Coray lab for my thesis work, where I continued my research in Alzheimer's immune system single-cell transcriptomics (Oh H., et al. *Molecular Neurodegeneration* 2021, DOI: 10.1186/s13024-021-00423-w) while also expanding into large-scale human plasma and cerebrospinal fluid proteomics to study how humans age (Rutledge J., Oh H., and Wyss-Coray T. *Nature Reviews Genetics* 2022, DOI: 10.1038/s41576-022-00511-7). We discovered that our internal organs age at different rates, and this has consequences for our susceptibility to age-related diseases, ranging from heart disease to Alzheimer's dementia (Oh H.S.-H. and Rutledge J., et al., *Nature* 2025, DOI: 10.1038/s41586-023-06802-1). We also found that the brain and immune system were key organs linked to long-term health and longevity in humans (Oh H.S.-H., et al. *Nature Medicine* 2025, DOI: 10.1038/s41591-025-03798-1). Lastly, we identified a pair of synaptic proteins in human cerebrospinal fluid whose levels could predict if and when someone would develop Alzheimer's dementia (Oh H.S.-H., et al. *Nature Medicine* 2025, DOI: 10.1038/s41591-025-03565-2).

We would like to know more about your career trajectory leading up to your current role. What defining moments channeled you toward this opportunity?

I found the scale and human impact of my PhD research fascinating and rewarding. At the same time, I felt frustrated at its largely correlative nature, which limited our ability to draw causal conclusions. This motivated me to return to the animal model experiments that first drew me to lab science so I could investigate the mechanisms underlying brain-immune system interactions in aging and Alzheimer's disease. I also felt a pullback to my original interests from high school of understanding the subjective human experience and working to treat conditions like chronic pain, which may not shorten lifespan but profoundly diminish the quality of life.

After exploring the literature and engaging in numerous conversations with scientists across various fields, I found a home for my interdisciplinary interests at the Brain-Body Institute and the Loeb Center for Alzheimer's Disease at the Icahn School of Medicine at Mount Sinai. As a postdoctoral fellow co-advised by Scott Russo and Alison Goate, I am currently pursuing several projects on brain-immune interactions in chronic stress, depression, and dementia, which span both animal models and human participants, including ongoing clinical trials. I am particularly interested in how psychological stress accelerates aging in peripheral organs and how signals from these organs can, in turn, rewire the brain to shape our emotional states and long-term health.

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?

Switching fields in graduate school from hematopoietic stem cell biology to Alzheimer's disease and aging felt quite risky. I was not a neuroscientist, and I had no prior experience with bioinformatics, so the first two years in the lab were a period of considerable exploration, especially during the COVID-19 pandemic. I struggled with self-doubt and often felt lost. However, one silver lining of the pandemic was that it provided me with the opportunity to focus intensely on learning how to code and apply what I learned in class to explore our lab's human omics datasets. I enrolled in Stanford's undergraduate courses in Programming Methodology, R for Biostatistics, and Linear Algebra over my first year, which was invaluable. I never liked programming in college because I lacked a clear purpose for it, but in graduate school, using programming to explore questions about Alzheimer's biology was so fun and exciting! When my plasma proteomics project on human organ aging began to show real promise, I decided to fully commit to it, a decision that ultimately transformed my scientific trajectory.

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

Over time, I have come to realize that it is difficult to commit to something that does not genuinely excite me fully. Even if a project is objectively important and interesting, if it does not resonate with me, it does not receive the attention it deserves. I have made a point to pursue projects that naturally spark my curiosity, and as a result, I find myself working harder without even realizing it.

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

I am currently focused on dissecting the bidirectional communication between the brain and peripheral organs in the context of chronic stress and depression. Major depressive disorder is not simply a disorder of the central nervous system; it is increasingly evident that immune cells and metabolic organs like the gut can amplify or dampen mood symptoms. Using large-scale proteomic and metabolomic profiling of blood from both patients and mouse models, I hope to identify peripheral proteins and metabolites whose levels track with, or precede, depressive-like behavior. I aim to test whether specific candidates emerging from these screens are causal in depressive-like behavior. Moreover, I am examining the molecular "fingerprints" of natural and pharmacological interventions, such as exercise and ketamine, to uncover mechanisms that can promote recovery from and resilience to chronic stress.

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

Ultimately, I hope these studies reveal novel mechanisms of brain-body communication that we can leverage to develop new therapies for diseases of human suffering.

What do you most enjoy in your capacity as an academic or research rising star?

I appreciate that academia values intellectual freedom, the ability to pivot toward new leads, and the opportunity to learn new skills, even if this means lower productivity during the early stages of a project. I am deeply grateful to my advisors for investing in my growth and learning.

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 you feel strongly devoted to?

As scientists, we celebrate those who think outside the box and make groundbreaking, unexpected discoveries. Yet, most funding agencies

Figure 2. Early days, imagining life from millennia ago. American Museum of Natural History, New York, USA. Sunday, 25 December 2005.

prioritize proposals backed by substantial preliminary data and that are relatively incremental in scope. Because researchers generally focus on what is funded, funding institutions must rethink their priorities. Supporting more high-risk, high-reward projects, especially from early-career investigators, could be genuinely transformative.

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?
Having recently moved to New York City, I have enjoyed exploring the vibrant food scenery. I love NY pizza and bagels! I also like jogging around Central Park, playing pickleball, and going to the movies.

Part 2: Hamilton Oh – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
Tall Korean boy.

Among your talents, which one(s) give(s) you a competitive edge?
Comfort in wandering, intense focus, friendly.

If you could change one thing about yourself, what would it be?
Less shy.

What is your current state of mind?
Excited to start something new.

What is your idea of perfect happiness?
Nature adventure, good food, and laughs with loved ones.

When and where were you happiest? And why were so happy then?
Being on a dance team in college. Community, abstract self-expression, physical fitness, and a high metabolism allowed me to eat a lot.

What is your greatest fear?
No love.

What is your greatest regret?
Not yet a regret because I still have time, but I wish I could play blues solo on the electric guitar.

What are you most proud of?
Living true to my values.

What do you consider your greatest achievement?
Doing and sharing science that people find valuable.

What or who is your greatest passion?
There are too many to pick from.

What is your favorite occupation (or activity)?
Eating.

What is your greatest extravagance?
High-quality extra-virgin olive oil and tomatoes from Italy.

What is your most treasured possession?
My box of memories.

Where would you most like to live?
I do not know yet. But I miss California.

[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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What is the quality you most admire in people?
Authenticity, kindness, leadership, humor.

What is the trait you most dislike in people?
Liars.

What do you consider the most overrated virtue?
Efficiency.

What do you most value in your friends?
Laughing together.

Which living person do you most admire?
The many people who work selflessly to make the world a better place.

Who are your heroes in real life?
My friends and family.

If you could have dinner with any historical figure, who would it be and why?
John Mayer is an amazing guitarist/singer/songwriter.

Who are your favorite writers?
Haruki Murakami and Roald Dahl.

Who are your heroes of fiction?
Spiderman and Anakin Skywalker.

What aphorism or motto best encapsulates your life philosophy?
Figure out what you want to do before what you want to be. Play with the data. Have fun.

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