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Michael C. Oldham: Clarifying the cellular and molecular architecture of the human brain in health and disease through gene coexpression analysis

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Michael C. Oldham, PhD, is a faculty member in the Department of Neurological Surgery and the Brain Tumor Center at the University of California, San Francisco (UCSF). Over the past twenty years, he has developed and applied novel computational and experimental strategies for studying the cellular and molecular heterogeneity of human brain samples in normal and pathological states. During his PhD with Dan Geschwind at UCLA, he performed the first genome-wide analysis of transcriptional covariation in the human brain, discovering highly reproducible patterns of gene activity corresponding to distinct cell types and states. After a brief postdoctoral stint with Steve Horvath at UCLA, he was unanimously selected as a UCSF Sandler Faculty Fellow, which provided him with R01-equivalent funding and principal investigator (PI) status in the new UCSF Broad Stem Cell Center. After completing his Sandler Fellowship, he was recruited to join the faculty of the Department of Neurological Surgery and the Brain Tumor Center at UCSF, where he applies the computational and experimental strategies he has developed to study malignant gliomas. At UCSF, he has served as the PI on multiple R01 grants focused on elucidating the cellular and molecular architecture of normal and pathological human brain samples. Dr. Oldham has also prioritized the creation of novel informatics resources that organize vast amounts of gene expression data and analysis results for the neuroscience research community. These efforts have convinced him of the need for new technology infrastructure to modernize scholarly communication around data analysis. In this Genomic Press Interview, Dr. Oldham is happy to share his unorthodox scientific and meta-scientific journey with our readers.

Figure 1. Michael C. Oldham, PhD, University of California, San Francisco, USA.

Part 1: Michael C. Oldham – Life and Career

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

I was born in New York City and I currently live in Corte Madera, California, 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 the suburbs of New York City in a family of physicians. My father, John M. Oldham, is a distinguished psychiatrist and past President of the American Psychiatric Association. My mother, Karen P. Oldham, was an internist at Columbia for many years, and her father, Bernard Pacella, was a distinguished psychiatrist and past President of the American Psychoanalytic Association. Other family members were also physicians and growing up, I assumed that medicine was also my path. However, that path was not to be.

I attended Duke University and graduated at the ripe age of 20 with a BS in Psychology and a pre-med focus. I had shadowed physicians, volunteered in the ER, taken the MCAT, and performed well. However, when it came time to apply to medical school, I could not bring myself to do so. It felt like something was missing, and I recognized it for what it was: I did not feel a strong, intrinsic desire to treat patients, and I knew that was a red flag. So, I stepped off the medical school conveyor belt with no Plan B.

I spent about six months traveling around Europe by myself after college, reflecting on what I might do instead, but mostly drawing blanks. When I returned to the States, I visited my best friend in San Francisco,

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where he was trying to make it as a rock star. Although I had not spent much time in California, I instantly fell in love with the Bay Area and decided it was where my future lay. So, I packed up my 1989 Toyota Camry and drove across the country to start a new chapter in life.

I needed to get a job, and my friend connected me with his college buddy, who worked at an advertising agency called Goldberg Moser O'Neill, located on Maiden Lane, just off Union Square in downtown San Francisco. The next thing I knew, I was a Media Planner managing multimillion-dollar advertising budgets on behalf of large corporations, such as Dell Computer and Symantec. It was a fun job, filled with young people and social activities at a time when the Internet was just being born. After a couple of years, I took a new job doing similar work at a company called Organic, which was one of the first website design shops in San Francisco. The company went public, and I thought I might strike it rich, but the market collapsed before I could sell any shares.

I had never expected to work in advertising. Although I had fantastic supervisors, learned a great deal, and formed strong relationships, the work was deeply unsatisfying to me. My professional unhappiness prompted me to revisit my academic studies in search of that spark, that feeling that comes from trying to understand something that stirs you in a way you cannot quite explain. I had always been fascinated by the brain and by language – the beauty of words, the evolution of their meaning over time, and the miracle by which infants acquire them. I started reading books about language and its evolutionary origins. In particular, I spent a considerable amount of time reading *"The Symbolic Species"* by Terrence Deacon, which helped galvanize my interest in this topic. I realized that I wanted to study something that was *at the root*: something that was fundamental to the human experience. It occurred to me that the question of how human language came to exist was synonymous with another, more neuroscientific question: What makes a human brain different from a chimpanzee brain?

Humans and chimpanzees diverged about six million years ago. Although our genomes are more than 98% identical, something happened during that time frame that set *Homo sapiens*, the knowing human, on a radically different evolutionary path, giving us cognitive abilities that are qualitatively distinct from those of all other creatures that have lived. Essentially, the genetic changes that gave rise to the modern human brain were the catalyst for life as we know it. What could be more root than that? I felt that spark and knew that I wanted to study human brain evolution. It was around that time that I figured out I could study the brain without pursuing an MD, and I applied to several neuroscience PhD programs on the West Coast.

It was a tough sell. I had been out of college and Science for over five years, and my research experiences were relatively limited. However, I was laser-focused and filled with passion, and sometimes that goes a long way. Although most programs rejected me, UCLA gave me a chance. When I met Dan Geschwind, who shared my newfound interest in human brain evolution, I saw the path before me and joined his lab.

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

After joining Dan's lab, I began working at the bench, performing Northern blots to compare the abundance of specific mRNA transcripts between human and chimpanzee brain samples. The work was analog and laborious, yielding many ambiguous results. Fortuitously, the first microarray datasets produced from human and chimpanzee brain samples were published at around the same time by Svante Pääbo's group. Rather than studying one transcript at a time, here was an opportunity to study thousands in parallel. I desperately wanted to learn how to analyze these data, but I had no computational skills or programming experience. Luckily for me, Dan collaborated closely with Steve Horvath, a UCLA faculty member who had trained as a mathematician but crossed over into biostatistics. Today, Steve is probably most famous for his discovery of the epigenetic clock. However, at the time, he had just developed a methodology called "Weighted Gene Coexpression Network Analysis", or WGCNA. Unlike differential expression analysis, which seeks to compare the mean expression levels of individual genes between two or more cohorts, gene coexpression analysis seeks to identify the most robust patterns of gene activity in a biological system. Working with Dan and Steve, I learned the rationale behind WGCNA and how to program in R. Within a few months, I was using it to analyze the microarray data that had captured my attention.

This effort was fruitful, revealing patterns of gene activity that were conserved between human and chimpanzee brains, as well as others that were not. We published our study in *PNAS* (my first paper, 2006, DOI: 10.1073/pnas.0605938103), and I had the green light from Dan to graduate. However, I did not want to! After completing my first study, I began to apply WGCNA to other, larger gene expression datasets derived from human brain samples. This led to a 'eureka' moment when I realized that many of the recurrent patterns of gene activity I was seeing corresponded to transcriptional signatures of different neurobiological cell types. Upon reflection, it made perfect sense: variation in the cellular composition of bulk tissue samples should inevitably drive the covariation of markers for different cell types. This central insight formed the basis for my second paper, published in *Nature Neuroscience* (2008, DOI: 10.1038/nn.2207), which described these signatures and demonstrated how gene coexpression analysis of bulk tissue samples can reveal optimal markers of cell types and states. This insight still forms the central thesis for my lab today.

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?

For many years, I have been tracking the meta-scientific literature on research reproducibility with growing alarm. Nearly all studies that have systematically examined this topic have reached the same conclusions: most published findings are not reproducible, and even those that are often have effect sizes that are much smaller than initially reported. As I internalized these findings, I started to feel despair. After all, if most of the findings we toil to produce cannot feasibly be reproduced, what is the point? I spent a considerable amount of time thinking about this. Like many seemingly intractable problems, a glimmer of a partial solution began to emerge when I broke the problem down into smaller pieces.

Although the reproducibility crisis has many causes, there is no reason in principle that data analysis, which is increasingly central to biomedical research, should not be completely reproducible. However, it often is not. In practice, data and code may be unavailable or only partially available if journal editors do not enforce this stipulation. Methods sections may omit critical experimental or analytical details and descriptions of data or metadata may not align between journal articles and data repositories. Resolving these challenges often requires timely feedback from the original authors, which can be uneven at best. These realities highlight important shortcomings in our system of scholarly communication and suggest a need for reform.

Motivated by these concerns, I joined a standing UCSF Academic Senate Committee on Library and Scholarly Communication. Now, as Vice Chair of that committee, I have launched a pan-UCSF Academic Senate Task Force on research data and metadata standardization, which I currently chair. The purpose of this Task Force is to define community standards for the packaging and description of data and metadata by UCSF investigators. Although this topic may sound dry, these standards are an essential prerequisite for more open and reproducible Science, more precise forms of biomedical knowledge representation, and more efficient forms of collaboration, teaching, and scholarly communication.

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?

I chose not to finish my PhD at the earliest opportunity (i.e., after my first major publication). Some people (possibly including Dan) thought this was a bit nuts. Instead, I spent two more years in the lab and produced a second publication that had an even greater impact. As a result of this choice, I was unanimously selected as a UCSF Sandler Faculty Fellow, which provided me with the independence and funding to establish my own lab almost immediately after graduating from graduate school.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
I did not have a full postdoctoral experience, as I was awarded the Sandler Fellowship only a few months into my postdoctoral work with Steve Horvath. However, the main habit I started with Dan and Steve, integrating patterns of gene activity across many independent datasets, remains the backbone of my lab's work today, as this practice increases statistical power and builds confidence in our findings.

Please tell us more about your current scholarly focal points within your chosen field of Science.
I was recruited by the Department of Neurological Surgery and the Brain Tumor Center at UCSF to apply my approach to adult malignant gliomas, which are notoriously heterogeneous and aggressive. It has been a fascinating transition into cancer biology, and I am grateful to have cultivated a unique perspective on gene activity in the human brain from my prior work. We have analyzed, integrated, and compared patterns of gene activity from vast amounts of neurotypical human brain samples and malignant gliomas. These efforts have focused our attention on vascular cells, which are difficult to isolate and capture for single-cell analyses. By comparing the vascular patterns of gene activity between normal human brains and gliomas, we have identified high-confidence molecular markers of glioma vasculature. Many of these genes encode cell-surface proteins that provide molecular 'zip codes' for gliomas that are accessible via the bloodstream. We are now advancing these targets in various translational directions, including for use as biomarkers and the development of novel therapeutic agents.

Of course, the information captured by coexpression analysis of human brain samples goes far beyond the vasculature. To organize and disseminate our findings, we have developed the OMICON platform (theomicon.ucsf.edu) to promote FAIR (**F**indable, **A**ccessible, **I**nteroperable, **R**eusable) research practices involving human brain gene coexpression networks. Currently, OMICON contains structured gene expression data for >17K bulk human brain samples (~10K normal and ~7K malignant glioma), which were collected from diverse public repositories and consortia. Using these data, we have identified ~100K gene coexpression modules, which have been extensively characterized via enrichment analysis with thousands of curated gene sets. All datasets, metadata, gene coexpression networks, enrichment results, and analysis steps can be browsed with an interactive workflow visualization tool, which promotes accessibility, reusability, and reproducibility by maintaining complete data provenance with unique identifiers. To promote findability, we have developed an advanced search engine that identifies datasets, samples, modules, and more by filtering standardized metadata. Through this functionality, OMICON aims to foster community and concentrate therapeutic efforts on reproducible analyses of transcriptional variation in the normal human brain and brain tumors.

What impact do you hope to achieve in your field by focusing on specific research topics?
Glioblastoma is a terrible disease. Despite the best efforts of a generation, we have not made significant progress in terms of patient care and outcomes. I hope our efforts can contribute to better outcomes for these patients. In a more general sense, I aim to develop new technology infrastructure to enhance the efficiency of biomedical research by enabling faster and more accurate data discovery, ensuring bioinformatic reproducibility, and fostering new forms of collaboration, teaching, and scholarly communication centered on data analysis.

What do you most enjoy in your capacity as an academic or research leader?
The thrill of discovery never gets old! But I am also blessed to work with talented people from all over the world who seek only to pierce the veil. It is a true source of joy to work closely with young people who are not only smart but also filled with curiosity, passion, and grit.

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?
We need to reimagine scholarly communication for the 21st century. For centuries, scientists have communicated their findings through long-form narrative journal articles. This is not how most kids today are trained to consume information, and I fear we will lose a generation of young scientists as a result. Furthermore, the reproducibility crisis is a canary in the coal mine. If that does not warrant transformative scrutiny, what will?

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 fortunate to live in Marin County, Northern California, where you are never more than five minutes from a trailhead. You will often find me walking alone in the woods, lost in thought. I am also fortunate to have a large group of dear friends from my early SF days who practice a consistent motto: ABC (always be celebrating!).

Part 2: Michael C. Oldham – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
I am determined, which helps me execute long-term plans effectively.

Among your talents, which one(s) give(s) you a competitive edge?
I like to think I have a lot of mental stamina. I can focus on a task for an extended period (even if I don't like it), and I don't give up on a problem until I have exhausted all possible approaches to solving it. I am also good at tuning things out (a trait I inherited from my mom!).

If you could change one thing about yourself, what would it be?
I wish I were more of an extrovert. I can turn it on when I need to, but it's not my natural state.

What is your current state of mind?
Tired! I am writing this at the International Conference on Brain Tumor Research and Therapy (ICBTRT) meeting in Japan, and my body is not sure what time it is.

What is your idea of perfect happiness?
The absence of stress and the presence of love.

When and where were you happiest? And why were you so happy then?
I subscribe to different flavors of happiness. There is happiness with friends, which tends to peak each year in the ephemeral and inestimable

[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.

Figure 2. Mike Oldham, in celebration mode.

magic of Black Rock City. There is also happiness with my family, which grows each year alongside my wife, Gwen, and our son, Evan. However, I would like to think that the happiest moments are yet to come.

What is your greatest fear?
Failure – especially if that results in being eaten by a giant spider.

What is your greatest regret?
I regret not having more self-confidence when I was young – but better late than never!

What are you most proud of?
The life I have created in the Bay Area, including my amazing wife, Gwen, our preternatural son, Evan, our lakeside home, and my faculty position in one of the world's greatest departments and research universities.

What do you consider your greatest achievement?
Scientifically, we have proposed a statistically motivated solution to one of the core problems in biomedical research: how to identify optimal molecular markers for cell types and cell states. I am very proud of this solution, which involves integrating patterns of gene activity corresponding to cell types or states across vast amounts of bulk data representing many billions of cells. Therefore, the results are highly robust and reproducible. But in life, nothing compares to raising a child.

What or who is your greatest passion?
I am a connoisseur of electronic music which I have listed to almost exclusively for the past 25 years.

What is your favorite occupation (or activity)?
My friends include many dancers and DJs (including me), and we gather regularly to dance and celebrate in beautiful spots around San Francisco and Northern California (see Figure 2).

What is your greatest extravagance?
I spend thousands of dollars a year on a new B3 vitamin and NAD^+ precursor called nicotinamide riboside. I discovered it while monitoring the scientific literature and came across a *Science* article (2016, DOI: 10.1126/science.aaf2693) showing that it extended the lifespan of aged mice. It turned out that this was based on previous work showing that nicotinamide riboside promoted Sir2 silencing and extended lifespan in yeast; Belenky P et al., Cell, 2007, DOI: 10.1016/j.cell.2007.03.024. Nicotinamide riboside has since demonstrated efficacy in treating diverse conditions across various model organisms and is currently in clinical trials for multiple indications—see: Berven et al., *Nat Commun* 2023, DOI: 10.1038/s41467-023-43514-6; McDermott MM et al. *Nat Commun* 2024, DOI: 10.1038/s41467-024-49092-5; Norheim KL et al., *Nat Aging* 2024, DOI: 10.1038/s43587-024-00758-1, and Shoji M et al., *Aging Cell* 2025, DOI: 10.1111/acel.70093. The topic of cellular aging and the role of NAD^+ in this process is fascinating.

What is your most treasured possession?
I am not a big consumer, but I do love my DJ controller. However, I do not treasure it as much as old photos of my friends and family.

Where would you most like to live?
Marin County, California! It is like the shire.

What is the quality you most admire in people?
Kindness.

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

What do you consider the most overrated virtue?
Piety.

What do you most value in your friends?
Loyalty.

Which living person do you most admire?
My dad! I do not think I have known anyone with more integrity.[2]

Who are your heroes in real life?
My family members each in their own way. Jane Goodall. And anyone who consistently practices kindness.

If you could have dinner with any historical figure, who would it be and why?
He may not be a historical figure to most, but I would choose Larry Harvey. He saw things in people and cultures that others did not, and his efforts have touched the lives of millions around the world in ways that are truly unparalleled and comparable to no one else I can think of.

Who are your favorite writers?
The sad truth is that after devouring novels for most of my young life, when I became a scientist, my reading diet shifted almost exclusively to science-related articles and news. But if I had to draw from the past, I might choose Emily Dickinson, Vladimir Nabokov, and Gabriel Garcia Marquez.

Who are your heroes of fiction?
Don Quixote and Frodo Baggins.

What aphorism or motto best encapsulates your life philosophy?
Nothing in life is to be feared; it is only to be understood. – Marie Curie.

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[2]The interviewee's father, Dr. John M. Oldham, is also featured in a companion Genomic Press Interview in *Brain Medicine*, 2025 — DOI: 10.61373/bm025k.0059.

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Dr. Michael Oldham disclosed that after he started taking nicotinamide riboside, he invested in shares of one of the companies that manufactures it.

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