Dana Alliance Members' Views: Eric Nestler

Eric J. Nestler, M.D., Ph.D., **is the Nash Family Professor of Neuroscience, Director of The Friedman Brain Institute, and Dean for Academic and Scientific Affairs at Icahn School of Medicine at Mount Sinai. His lab uses animal models of depression and addiction to identify the ways in which long-term exposure to drugs of abuse or stress changes the brain to lead to addiction- or depression-like syndromes.**

Mount Sinai is very active during Brain Awareness Week. Why is outreach such a priority? What advice do you have for neuroscientists looking to participate in educational activities aimed at the public?

It is very important for the general public to be excited about the promise of science, biomedical research in particular. I fear that too many of our primary and secondary school students are bored by science and mathematics—the way we currently teach it—and zone out whenever the topic comes up. Yet the public's support is essential for us to maintain robust funding for the National Institutes of Health (NIH) and to continue the quest to find treatments, cures, and preventive measures for the range of conditions that affect humankind. We are indeed fortunate to have a bipartisan consensus in the U.S. Congress to support NIH, with more than $7B in additional funding allocated over the past three fiscal years.

Neuroscience is especially important. Five out of the top ten causes of disease burden worldwide are brain disorders: depression, dementia, stroke, psychosis, and addiction. In fact, depression is the leading cause of disability across the globe. Today's entire Medicare budget will be consumed solely by caring for individuals with dementia within a couple of decades if no dramatic improvements in treatment or prevention are devised; dementia will consume our society. This central importance of neuroscience is reflected in the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative, a priority of NIH funding. This is a spectacularly exciting time for neuroscience research, given several technical advances in studying the molecules, cells, and circuits that comprise the brain and how they interact to mediate all brain functions as well as the brain's ability to learn and adapt over time.

It is a responsibility for every neuroscientist to help spread the word to the general public. They can do so by writing OpEd articles for local newspapers, by volunteering to teach public school students about the brain, by speaking at events sponsored by patient advocacy groups, and by getting involved in—and leading—their institution's outreach efforts to the community. The Society for Neuroscience provides a uniquely effective vehicle through which neuroscientists can get involved and make a difference. Some of us may want to leave this to others, but that is an enormous mistake. Each of us must do our part in showing our local and national communities the excitement of neuroscience and its importance for the future physical and economic health of our country.

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You just ended your term as president for the Society of Neuroscience (SfN). What were your goals as president?

It was the privilege of a lifetime to serve as SfN president. I recall the first SfN annual meeting that I attended. This was in 1978 when I was a graduate student. The opportunity to present my work and network with other trainees as well as with leaders in the field provided a critical launchpad for my career. It is very exciting and heartening for me to see SfN continue to play this role, offering far more now than decades ago, for my current students and postdocs.

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My goals at SfN were severalfold. First, I wanted to be a good steward for the Society during a time of particular turbulence. President Trump was elected one week before my term began and this created a great deal of uncertainty in the scientific community. I wanted SfN to continue to articulate its principles concerning the importance of a global scientific community, as today's advances in neuroscience and biomedical research in general demand worldwide collaboration. I wanted to emphasize the importance of promoting a scientific community of diverse backgrounds and perspectives, because we know that a diverse group of people tackle difficult challenges better. I also was committed to increasing the Society's investment in our young trainees through greater funding of travel and training awards. Finally, I wanted to redouble the Society's commitment to public outreach for all of the reasons outlined above. And it's important to emphasize that our ability to work on these goals depended on a financially healthy Society with the strong support of its ~37,000 members worldwide.

You have attended SfN Hill Day. Why is it important for individual scientists to connect with lawmakers? What do you hope attendees took away from this year's event?

Yes, I have greatly enjoyed the opportunity to participate in SfN Hill Day. Each year, Hill day provides a venue for young members of SfN, including participants in the Society's Early Career Policy Ambassadors Program, to visit with members of Congress and their staffs. It is also important to have more senior members of our nation's neuroscience community be actively engaged. I hope that our attendees this year took away much the same as what I hope our Congressional representatives took away, that neuroscience—and biomedical research in general—is bipartisan, that Republicans, Democrats, and Independents get the same illnesses and need the same treatments. In fact, our hope is that bipartisan consensus around biomedical science could serve as a catalyst for political opponents in the country to work together to solve the nation's other problems.

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Your lab studies the molecular mechanisms of addiction and depression. What are some common misconceptions about depression/addiction? Are you optimistic about the future of treatment for depression/addiction?

Addiction and depression are viewed historically as psychiatric disorders. As such, there remains the broad misconception by many that these conditions are somehow less medical—less physical, less real—than the other major health challenges of our time, such as cancer, cardiovascular disease, diabetes, and infectious disease. Yet addiction and depression at their core are brain disorders mediated by deleterious molecular and cellular changes that a drug of abuse or stress induces in a vulnerable brain, just as cancer, cardiovascular disease, diabetes, and infectious disease are influenced not only by physical factors but also by psychological, social, and cultural factors.

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I remain optimistic that we will succeed in developing dramatically improved treatments for addiction and depression. However, I must admit to being frustrated that my generation of scientists has not been able to make these clinical advances over our 30 or so year careers. We've learned an enormous amount about the brain—really a staggering amount over these three decades—and we're beginning to learn a great deal about the brain's illnesses as well. Although I am humbled by the magnitude of the challenge to translate these advances to the clinic, we must not despair. This slow progress simply reflects the unique complexity of the brain and its diseases.

I recall being in medical school forty years ago and hearing my professors talk about "molecular medicine"—that we were close to a time when a cancerous growth could be removed from someone, profiled molecularly, and a treatment (such as an antibody) developed to target that person's tumor. Today we call that approach precision medicine. Well, we are now at long last beginning to see such precision medicine treatments for cancer and certain other diseases, which are far simpler than brain disorders. If it took four decades to get there for cancer, it will simply take much longer for the nervous system. In fact, I am heartened by the transformational advances in our ability to study the brain at the molecular, cellular, and circuit levels—advances that we didn't even imagine decades ago. I am confident that with advances such as these, neuroscientists will begin to tackle brain disorders and I still believe that I will see such first advances in my lifetime (and I'm 63!).

You are on the Depression Task Force for the Hope for Depression Research Foundation (HDRF) with other scientists, including DABI members Huda Akil, Helen Mayberg, and Bruce McEwen. (DABI vice-chairmen Eric Kandel and James Watson are on the Scientific Advisory Council.) What is the mission of HDRF and how does the Depression Task Force work towards that mission?

The HDRF has been a unique opportunity for me. I joined the group about six years ago. It provides the opportunity for eight basic and clinical neuroscientists to work with one another in a completely open and collaborative manner. Each of us approaches the question of depression—its neurobiological basis and need for improved treatments—with complementary experimental methodologies, which we share across laboratories. Members of our labs have gotten to know one another very well, which has built an unusual level of trust and collaboration.

Large datasets, such as RNA-sequencing findings, are deposited in a joint Data Center and accessed by teams from numerous laboratories who undertake independent analyses. I would recommend a recent review article that the eight of us wrote together, "Treatment resistant depression: A multiscale, systems biology approach," for a more detailed elaboration of how our group integrates findings coming from human genetics, human brain imaging, and brain

circuit, genomic, and epigenomic analyses in a wide range of mouse and rat models to identify key molecular pathways and circuits involved in depression and its treatment. In fact, our group has already advanced several new small molecules for clinical testing. It's too early to know whether these new treatments will work—they probably won't—but this illustrates how a collective, unselfish effort can succeed in mining basic science findings for clinical advances while simultaneously taking advantage of new clinical observations for mechanistic exploration in animal and cell models.

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You were an author on a recently published study that found that early life stress in mice can cause depression in adulthood. Can you tell us a little more about the results and their implications?

Thank you for mentioning this study, led by Catherine Peña, Ph.D., a very talented postdoctoral fellow in my laboratory. This underscores something which we all know, namely, that any lab's success depends on the outstanding graduate students and postdocs who do all of the hard work, and I have been very fortunate to have had so many outstanding people work with me over the years.

My lab and others have been interested for some time in the question of how early life experience changes the brain for a lifetime. One type of mechanism, which we refer to as epigenetics, would involve changes not to DNA sequence but to the packaging of DNA within the nucleus of particular cells in the brain. This is by analogy with developmental biology and cancer, where certain types of such chromatin modifications (chromatin refers to the DNA and protein constituents of the cell nucleus) once they occur are permanent. Perhaps similar modifications induced in brain cells by an early life experience similarly last a lifetime.

Cate addressed this question by developing a mouse model where removing mouse pups from their mothers for three hours a day—but at a precise period during early development—and reducing the amount of bedding material available to the mothers rendered the pups more susceptible to stress in adulthood. Interestingly, the adult animals showed no detectable behavioral abnormalities in the absence of that second stress, but they possess a latent vulnerability that was revealed by the second hit. To identify the molecular basis of this latent vulnerability, Cate performed RNA-sequencing on the ventral tegemental area (VTA), one of the brain centers rich in the neurotransmitter dopamine, since this brain region has been shown to be important in emotional development. Cate found that exposure to early life stress induced lifelong changes in gene expression in this brain region that in part resemble the gene expression changes that severe stress induces in normally-reared animals. It appears that early life stress "primes" gene expression in the VTA to be in a severe stress-like state. Cate went on to show that one prominent mechanism underlying this phenomenon is a transcription factor called OTX2, which has been implicated in VTA development but not previously in stress responses. Cate showed that early life stress suppresses OTX2 expression in VTA dopamine neurons transiently around the stress period, and that although OTX2 levels themselves rapidly return to normal, the genes controlled by OTX2 show permanent impairments in their expression. Our hypothesis is that the transient loss of OTX2 induces "chromatin scars" at these genes, which are lifelong, and we are now working to identify the nature of these chromatin scars, which could be targets for future therapies. Meanwhile, Cate and others in the lab have found additional mechanisms that operate in different brain regions and that, although male and female pups show similar behavioral responses to early life stress, the gene expression abnormalities contributing to lifelong stress susceptibility are largely different between the sexes. This argues strongly for looking for biological explanations for depression, and novel treatments, in a sex-specific manner, as we may ultimately find that depressed men and depressed women respond optimally to very different treatments.