TRAN1-16262
Supporting Letters for NysnoBio

Table of Contents

CIRM TRAN1-16262
April 26, 2024

Dear CIRM and ARS Committee members,

This letter is provided by the applicant, NysnoBio GT Neurology, in support of our TRAN1-16262 application. In this letter we (1) summarize letters of support sent by our collaborators and PD experts and (2) provide additional clarity on points highlighted in our unanimously positive reviews by the GWG CIRM panel. First, we would like to thank the GWG and CIRM personnel for the thorough work involved in the careful review of materials and the ARS committee for the opportunity to provide supporting letters for our application.

NysnoBio's mission is to advance therapies to prevent the progression of relentless degenerative diseases, specifically Parkinson's Disease, which affects up to 10 million people worldwide, and over 116,900 people in California alone (as of 2021) equally from all cultural and racial backgrounds (https://www.michaeljfox.org/publication/california-funds-parkinsons-disease-registry-advocacy-and-support-michael-j-fox). We are a California company and are organizing our initial clinical trials at UCSF, to enroll Parkin-PD patients from California. Our approach is to target genetic forms of disease as initial proof-of-concept for human activity, translating these genetic cures to additional patient populations as etiology-specific biomarkers become available. Genetic cures have transformed the landscape of oncology, and we are confident that a similar transformation is on the horizon for degenerative diseases of the CNS.

1. Letters of Support:
   a. **Dr. Hiral Shah, MD**, a movement disorder specialist at Columbia University specifically focused on outreach to underserved communities of color (https://www.neurology.columbia.edu/profile/hiral-g-shah-md)
   b. **Ms. Tyaisha Dillon**, an African American PD patient with Parkin-Mutation linked Young Onset Parkinson's Disease (https://www.parkinson.org/living-with-parkinsons/stories/tyaisha-blount-dillon)
   c. **Dr. Chantale Branson**, a movement disorder specialist at Morehouse University and Parkinson's Outreach Advocate for BLAAC-PD and the Parkinson's Foundation (https://www.msm.edu/about_us/FacultyDirectory/Medicine/ChantaleBranson/index.php)
   d. **Dr. J. William Langston**, Professor of Pathology and Neurology at Stanford University, NysnoBio SAB member and one of the world's preeminent experts on Parkinson's Disease https://profiles.stanford.edu/james-langston)
   e. **The Michael J Fox Foundation for Parkinson's Research**, a foundation created with a mission to cure Parkinson's Disease (https://www.michaeljfox.org/)

2. Provide clarity on points highlighted in our unanimously positive reviews by the GWG CIRM panel.
   a. The GWG review highlights noted that NysnoBio's work is clearly providing a transformative therapy for genetic PD patients, and noted additional data can demonstrate translation to non-genetic patient populations. In the letters from Dr.

Langston and the MJFF, the rationale for testing Parkin's role in the larger sporadic PD population is discussed. We agree that we need to demonstrate clinical efficacy of our product in genetic patients first, and that is the basis of our TRAN1 application. Once we have clinical proof of concept to restore movement and halt disease progression in Parkin-PD, we can move to additional patient populations with substantiated justification for clinical response. Because mitochondrial damage is a known etiology for PD and Parkin's mechanism of action is to remove mitochondrial damage, our human proof of concept in genetic patients will provide clinical biomarkers and insight into the impact of removal of mitochondrial dysfunction to reverse the course of PD. Underserved communities working with pesticides are being exposed to toxins that create mitochondrial damage here in California.

b. The GWG review highlights our excellent CMC plan and clear advancement strategy to successfully complete the PRE-IND Meeting in the next 12 months. As a part of the plan, we have tested drug substance (NB001) produced from our SF9 process development work in cellular potency assays, and for in vivo endpoint analysis in rodents and non-human primates. While the preliminary data in the proposal was from our first research lot of NB001produced in HEK cells, we have subsequently tested NB001 from our process development work produced in Sf9 cells. Our Sf9 lot(s) of NB001 have titer, infectivity, potency and in vivo efficacy and target area coverage equivalent or superior to our research lot. For our pre-IND meeting that is the goal of our TRAN1 application, we will only be submitting data obtained using the NB001 produced from our process development work.
c. The GWG review component of DEI strategy in our application was average, and our intent was to outline an authentic working strategy for outreach to underserved communities with YOPD to not only create diversity for our own successful clinical trials, but to raise awareness of YOPD and genetic testing to empower these underserved groups to advocate for themselves in their own health care. To provide more clarity on the specific ongoing activities and plans for NysnoBio outreach, Dr, Shah, Ms. Dillon, and Dr. Branson have provided letters of support articulating our ongoing activities and planned use of funds if awarded this CIRM TRAN1 grant. The outreach efforts already ongoing are a high priority to begin building the basic tools and relationships needed to create major impact, build trust, and change the public perception of Parkinson's Disease from an "Old White Man's Disease" to a debilitating disease that affects all people regardless of ethnic or cultural background.

We want to thank the GWG, CIRM and the ARS for this opportunity for funding through the TRAN1 program. Funds awarded to NysnoBio will help to transform the treatment of Parkinson's Disease, in California and the world, and we look forward to the ARS review committee decisions soon.

Sincerely,

Jennifer A Johnston

Jennifer Johnston, PhD | CEO / Founder

NYSNO bio

nysnobio.com

NEW YORK PRESBYTERIAN HOSPITAL
COLUMBIA-PRESBYTERIAN MEDICAL CENTER

COLLEGE OF PHYSICIANS & SURGEONS OF COLUMBIA UNIVERSITY

Hiral Shah, M.D.
Assistant Professor of Neurology
Division of Movement Disorders
Global Mental Health Scholar, Columbia University
Global Health and Aging Policy Fellow, 2015-2016
Email: hs2412@columbia.edu

April 19, 2024

Dear Selection Committee,

I am writing on behalf of myself, NysnoBio, and the PD Movers, in support of the application submitted to develop parkin-based genetic therapy for Young Onset Parkinson's Disease (YOPD) by Dr. Jennifer Johnston.

As background, I am a faculty member in the Department of Neurology at Columbia University since 2013, and currently serve as the Medical Director for the Parkinson's Foundation Center of Excellence. My responsibilities have included supervision and training of residents and fellows in movement disorders in the ambulatory setting, along with oversight of the clinical operations and outreach efforts of our center. I have served as a consultant for WHO and part of the steering committee that published "Six Action Steps to Address Global Disparities in Parkinson Disease: A World Health Organization Priority" (JAMA Neurol 2022). And, I am the Founder of the PD Movers, a group of individuals who identify as African American/Black and are either living with Parkinson's disease (PD) or are care partners, who partnered with Columbia University, Teacher's College and St. Luke A.M.E. Church, to develop this resource.

I met Dr. Johnston as we both serve on the Young Onset Parkinson's Network Advisory Board. After our first meeting, we immediately connected over our mutual recognition of the need to develop tailored strategies to reach under engaged communities in order to effectively address existing health disparities in Parkinson's disease treatment and care. Since our initial meeting, we have met more than 8 times, and I have been energized by Dr. Johnston's interest and desire to be forward-thinking and willing to learn about how to best approach and partner with under engaged communities given my work with the PD Movers.

The PD Movers developed the first-of-its-kind educational resource – *The PD Movers: We Keep Moving, Living and Thriving with Parkinson's disease* (https://www.neurology.columbia.edu/patient-care/specialties/movement-disorders/pd-movers-we-keep-moving-storybook) – which is a compilation of first-person narratives accompanied by vibrant illustrations and educational material that allows the reader to become familiar with the lived experience of those from the AA/Black communities who have faced a diagnosis of PD. This book has allowed the breaking down of barriers to accessing culturally-sensitive educational resources and opened doors to organizations and communities who are now interested to learn more about Parkinson's disease. The academic partners have shared this resource over 10,000 times and

participated in numerous speaking opportunities at national and international venues to highlight this work as a model of community engagement. The A.M.E. Church has hosted a District Level Workshop based on the PD Movers book and the New York Conference Women's Missionary Society hosted a Workshop on Parkinson's disease for 70+ missionaries in the NYC area. This work has been described and published in Parkinsonism and Related Disorders ("Community-based participatory research approach to address healthcare disparities confronting members of the Black Diaspora with Parkinson's disease", Feb 2024). What started as an opportunity for individuals with Parkinson's and their caregivers to share their experiences has resulted in an organic upwelling of support, from those living with Parkinson's disease, their families as well as organizations. Underserved communities lack resources that they identify with, and this book has helped to create heightened awareness of Parkinson's disease in communities of color, instrumental to addressing health care gaps.

With this funding, I see the opportunity to further amplify this approach and focus on those living with YOPD who face a number of unique challenges including: concerns of loss of employment, social isolation, and lack of community connection. With the support of the CIRM, we can showcase the voices of those living with parkin PD from the AA/Black community, including Ms. Tyaisha Dillon. By creating resources in partnership with community members, like Ms. Dillon, we can produce unique, engaging, and impactful materials which will resonate with the community and increase awareness of the importance of genetic testing in Parkinson's disease and its impact on the development of therapeutics. We intend to develop a video about YOPD and genetic forms of the condition, the genetic testing process, and the potential impacts by sharing Ms. Dillon's story and documenting the process of genetic testing. We intend to disseminate the video through the established robust network of individuals and organizations engaged in the task of addressing health disparities in Parkinson's disease that have been partners with the PD Movers including: industry partners (such as Davis Phinney Foundation, Parkinson's Foundation, American Parkinson's Disease Association, The Brian Grant Foundation), Community Partners (Special Interest Group – Black Diaspora, co-led by Bernard and Denise Coley), Support Group Leader's Alliance (an organization of 10 support group leaders nationally who work with AA/Black individuals and care partners with PD), the Office of Faith Based Initiatives that coordinates activities for Faith Leaders in the five boroughs of New York City, as well as the A.M.E. Church networks locally and nationally. Further, Columbia University is already a site for PD GENEration (a Parkinson's Foundation sponsored research study that provides free genetic testing examining the 7 most common risk variants for PD, along with access to a genetic counselor, and importantly results), and I am a collaborator of Dr. Chantale Branson who is leading efforts at Morehouse College to increase the diverse recruitment of participants for this study.

The impact of this campaign will not only improve awareness and engagement by community members, as evidenced by Ms. Dillon's experience (she has spoken at two events, and after sharing her story, there was 100% participation by the participants in genetic testing procedures), but also inform industry and academic partners of the lived experience of those from the AA/Black community living with YOPD. These individuals are often unheard and unseen, perpetuating misconceptions and inadequate approaches to reach minoritized communities.

I strongly support this application and I hope you recognize the immense value and strategic thinking that Dr. Johnston has included to reach under engaged community members who are living with YOPD and are unaware of their genetic status, or lack access to diagnostic testing. I have learned so much on my journey with these patients and their caregivers – and the critical need to uplift the voices of the community, recognize the importance of representation, and need to build trust to encourage research participation readiness. With the support of CIRM, we will be able to reach and teach individuals in the

community so that they can be empowered with the knowledge of their genetic status and contribute to the development of therapeutics to ultimately cure individuals of this debilitating condition.

Sincerely,

Hiral Shah, M.D.

Dear California Institute of Regenerative Medicine (CIRM),

I'm reaching out, not just as an individual, but as a voice for women and people of color living with Young Onset Parkinson's Disease (YOPD). YOPD affects various communities, but for women and people of color, the journey of diagnosis, accessing care information, and tailored therapies is even more daunting. Let's address these challenges together.

Growing up, my parents instilled in me the importance of standing up for what's right, especially for underserved communities. They marched for civil rights, ensuring a better future for generations to come. Their dedication to service shaped my own journey, as I witnessed my father's commitment to helping the underserved youth in Baton Rouge, Louisiana, and my mother's resourcefulness and advocacy as a Librarian. Our family valued community service, education, hard work, having fun and keeping your medical problems to yourself.

My last year in graduate school, I started an internship with the United States Forest Service, around that time, I began experiencing my legs feeling very heavy and I had started dragging my feet or shuffling, like the walking dead. Feeling the need to conceal my condition, I'd discreetly handled the episodes by pretending to tie my shoe or retreating to a secluded spot in the office or in the forest. Despite my efforts to conceal my affliction, the progression of the illness made it increasingly difficult to do. One day my supervisor, Mae Lee Hafer, caught me whimpering in the restroom due to the horrible pain of dystonia in my legs and feet. I vaguely remember what she said including: " don't be embarrassed"; "you're not going to lose your job"; and something about "compassion and caring".

For the next 8 to 13 years, I battled this dreadful illness almost entirely on my own, visiting multiple doctors in search of an accurate diagnosis. It wasn't until I decided to take charge of my own healthcare that things began to change. I discovered that my insurance plan did not require referrals, so I started declining them. I also began researching doctors' backgrounds, choosing those who were known for their innovative and collaborative approaches to patient care.

That's how I found Dr. Dumor. His attentive care and advocacy, including pushing for me to get treatment at Washington University, transformed my approach to managing my health and ultimately changed my life.

Dr. Dumor attentively heard me out when I voiced concerns about my elevated creatine levels and described how my body was failing. He even scolded me by saying "you need to walk" when he caught me using an electric scooter at Walmart. I watched and learned his communication style as he advocated for me to receive treatment at Washington University, a renowned Parkinson's Foundation Center of Excellence back then. Dumor's steadfast determination and refusal to yield in the face of obstacles, such as navigating the complexities of patient admissions to the treatment center clinics, garnered admiration from his peers and gratitude from his patients. His unwavering confidence proved instrumental in empowering me to break free from years of silence surrounding my health. While Dr. Dumor collaborated with other physicians to ascertain my diagnosis, I also took proactive steps towards my healing journey. I commenced juicing greens and engaged in workouts under the guidance of my trainer Christina Fike at Feel Good Fitness in Rolla, Missouri. She meticulously tailored daily workouts that not only increased my muscle strength; but also gradually alleviated my dystonia symptoms.

Finally, about Thirteen years after I experienced my first symptom, I was officially diagnosed with Dopamine Responsive Dystonia with Parkinsonism, and about two years later, I was diagnosed with Young Onset Parkinson's disease.

As a child and young adult, I wondered why it was taboo for African Americans to discuss their medical issues. I recently had a discussion with my father about the state of healthcare before the 1960s. He informed me that in the 60's much of the United States was rural and many African Americans lived in remote areas, working as sharecroppers, caregivers, or teachers. Many communities during this time were geographically isolated which made it difficult for individuals to access regular healthcare and routine doctor visits. Additionally, employers put a greater emphasis on productivity rather than the health of employees, which played a role in this neglect.

My father also said it wasn't solely fear that kept the underserved from seeking healthcare or demanding better services. Many people simply weren't educated about the importance of regular healthcare and preventive medicine. The lack of information and awareness about health-related issues meant that seeking medical care wasn't always seen as a priority, and in some cases home remedies replaced proper care. Fortunately, the civil rights movement helped change this dynamic. Leaders like Martin Luther King Jr. called for equal rights and was a start to us accessing better healthcare. Military veterans have also advocated for better healthcare as well.

Sharing your health history with your family can indeed be crucial for their well-being, much like how "see something, say something" is vital to public safety. It's all about promoting safety and awareness in different aspects of life. Not sharing my family's health history has had a detrimental impact on me. Had I been aware of any familial history concerning conditions such as Parkinson's, commonly referred to as "the shakes," it might have spared me from enduring an extended period without a diagnosis. Luckily, I have found that positive side of my struggle. I have discovered that sharing my story at the right time can be therapeutic and offer learning opportunities.

Over the last five years I have been committed to empowering and encouraging others to take control of their health by accessing information about their specific disease and advocating for themselves. I have shared my story on several platforms including:

BDO
BlackDoctor.org

My academic background is science and engineering, so when I had the opportunity to work with the Parkinson's Foundation (PF) to participate in the Parkinson's Disease (PD) Generation genetic study; it was an automatic yes. I took the test for the good of science and the people it would help. I never imagined that a simple test would bless me in a much greater way.

In September 2023, I spent a weekend learning how to become a Parkinson's Research Advocate. At the training we talked about the many reasons why African Americans do not feel comfortable participating in studies. We also listened to Dr. Chantal Branson describe the PD Generation study and why we should be interested in participating in it. Branson indicated that Parkinson's research was advancing and that the results of the genetic tests could facilitate the development of patient specific treatments. After I took the test, I learned that I had YOPD due to mutations in the Parkin gene. I then decided to share my experience taking the test and my test results with my fellow Research Advocates in training. I was very surprised after telling my story, that we had 100% participation. I also shared my testing experience at a Community Conversation's event at Emory Brain Health Center participants were African American and again we got 100%. Given the significant reluctance within the African American community to engage in scientific studies, my encounters underscored the importance of persistently sharing our narratives.

After I became a Research Advocate, Dr. Hiral Shah introduced me to Dr. Johnston, and we instantly bonded over the shared desire to develop a way that the underserved community could understand the urgency and importance of being involved in Parkinson's Genetic studies. Through our plan to raise awareness and provide access to these tests, we can ensure that everyone, regardless of background, can benefit from early detection and personalized therapies.

The funding provided by CIRM for the work I am doing with Dr. Johnston to outreach to underserved communities to raise awareness for genetic testing will advance precision medicine and empower YOPD patients to advocate for themselves; and enable the development of new therapies. Together, let's continue the fight for health equity and better health for all.

Sincerely,
Tyaisha Dillon
@tbdillon
http://tbdillon.com

Morehouse School of Medicine
Department of Neurology

Chantale Branson, MD, MSCR, FAAN
Associate Professor of Neurology
Movement Disorders Specialist
Program Director, Neurology Residency

Dear California Institute of Regenerative Medicine (CIRM),

I am a board-certified neurologist with specialty training in movement disorders at Morehouse School of Medicine to understand better racial inequities in the diagnosis and treatment of Parkinson's Disease. My recent publications (for example, Branson and Saint-Hilaire, J Neurol Disord 2017, 5:2) have highlighted disparities, and I spend considerable time working to engage in outreach efforts to serve the PD patient community better. Through these efforts, I have met Dr. Hiral Shah, who is also working to increase awareness of disparities in underserved communities of gender/color, and we are working together to accelerate our efforts to help patients. One such patient is Tyaisha Dillon, whom I met at a Parkinson's Foundation (PF) genetic testing outreach event in Atlanta in 2023. Tyaisha is a trained PD advocate with the PF. After getting her genetic testing results, she realized that she wanted to engage in helping others realize that gaining access to genetic information provides empowerment about their disease. Working with Tyaisha and Dr. Shah, we are creating a robust network of outreach and advocacy.

Tyaisha and Dr. Shah have introduced me to NysnoBio and their genetic approach to treating Parkin-based forms of PD. I am excited to work with companies developing genetic therapies for this degenerative disease, like NysnoBio, because they treat an underserved community of patients (young) and are actively engaged with ambassadors like Tyaisha and Dr. Shah to engage communities of color and women. Genetic forms of the disease provide insight into general disease mechanisms, providing a translational pathway for our work in underserved communities of young genetic patients to chart the way forward for all PD patients. Parkin mutations affect all ethnicities equally, so including diverse patients will be necessary for clinical testing and validation of the therapy in humans. Nysnobio is working hard to prepare a diverse patient population for treatment.

I look forward to working with Nysnobio, Dr. Shah, and Tyaisha Dillon to achieve these goals through our outreach efforts.

I wholeheartedly endorse the funding of the work in this proposal and eagerly anticipate participation in genetic testing outreach activities in underserved communities of color with this team.

Dr. Chantale Branson, MD, MSCR, FAAN
Movement Disorders Specialist
Associate Professor of Neurology
Morehouse School of Medicine
Atlanta, GA

STANFORD UNIVERSITY

April 23, 2024

California Institute of Regenerative Medicine (CIRM) Letter of Support
TRAN1-16262

To Whom It May Concern,

I am writing to you on behalf of myself and as an SAB member of NysnoBio, a company developing a Parkin-based genetic therapy for Young Onset Parkinson's Disease (YOPD).

My background as a neurologist and scientist has been as one of the founders of modern Parkinson's disease research, both clinically and in the research lab. I founded the Parkinson's Institute (PI) to advance clinical and basic research in Parkinson's disease and related disorders and have provided fundamental insights into many aspects of PD. In our clinic at the PI and now at Stanford, I have been involved in almost every Parkinson's Therapy Trial in some fashion and have seen that disease-modifying therapies have yet to succeed in the clinic. As we have advanced our understanding of PD, we have learned, much like cancer in the field before us, that the key to making progress is to start with the genetic forms of the disease. The genes provide tools to understand how this widespread disease affecting millions of diverse people begins and point to pathways aimed at halting and possibly even reversing reverse the disease course.

At NysnoBio, their team is leveraging the most common young onset genetic form of PD, caused by mutations in the Parkin gene, to create a Parkin gene therapy that has the potential to reverse the course of the disease in young patients. If this therapy works to improve movement in these genetic patients, it will likely translate into a potential therapy to restore movement in additional groups of non-genetic patients. This is because environmental toxins causing PD also affect the pathway that Parkin regulates, demonstrating a clear connection ranging from environmental causes to genetic forms of the disease. There is a desperate need for new therapeutic approaches in PD, and because genetic mechanisms of disease provide a view into pathological mechanisms of disease pathogenesis, our highest priority should be to advance genetic targets to human testing. The Parkin gene is the most validated gene in PD because it is 100% penetrant in homozygous patients, and the mechanism of action of the gene in the disease process is well understood. Dr. Johnston has been at the forefront of research on the Parkin gene and protein function, and throughout her career has been focused on advancing PD therapeutics. Her depth of knowledge in this field is extraordinary, her dedication and persistence are exceptional, and the network of PD researchers on her team provides expert advice on all aspects of the therapeutic advancement pathway.

I have known Dr. Johnston, the founder and scientific leader of NysnoBio for over 20 years. She was one of the

first scientists I brought onto the scientific review board for the Michael J Fox Foundation over 20 years ago and we have worked together on countless Parkinson's Disease projects over the years, at my Parkinson's Institute, at her companies, and now with my role as Professor at Stanford University and SAB member at NysnoBio. Finally, as a woman in science, Dr. Johnston has been an unfailing advocate for diversity in research and development of therapies so that all patients can find relief from the relentless progression of these devastating degenerative diseases.

It is with the strongest of advocacy that I support the funding of the work in this proposal, to continue the momentum of the program to the clinic without delay.

Sincerely,

J. William Langston, M.D.
Clinical Professor of Neurology and Neuroscience, and of Pathology
Associate Director of the Stanford Udall Center, Department of Pathology.
Stanford University School of Medicine
Clinic: *Stanford Neuroscience Health Center*
(Rosalyn Versoza, Nurse Coordinator, Ph: 650-498-3230)
Office: Neurology/Movement Disorders
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Pathology Department: 650-497-1276

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

Dear California Institute of Regenerative Medicine (CIRM),

I am writing to you on behalf of The Michael J. Fox Foundation for Parkinson's Research (MJFF) in support of NysnoBio, a company developing a Parkin-based genetic therapy for Young Onset Parkinson's Disease (YOPD).

Since launching in 2000, MJFF has deployed more than $1.75B to accelerate research leading to critical new therapies for people with Parkinson's disease (PD). Genetic discoveries, including identification of mutations in the Parkin gene linked to PD, have exponentially expanded our understanding of disease pathogenesis, and paved the way for many potential treatments in development today. A key goal of MJFF funding is to de-risk promising approaches through early testing hurdles to increase confidence among potential future investors and partners able to carry a program forward. Our support to Dr. Jennifer Johnston and NysnoBio has helped her team explore neural network patterns as possible novel biomarkers in Parkin-associated PD and accelerated moving her Parkin gene therapy program toward IND to help prepare the program for future clinical testing.

Dr. Johnston has been a scientific advisor to MJFF since 2002, participating in and leading several workshops and reviewing numerous grant applications. In 2014, we awarded Dr. Johnston the J. William Langston Prize, recognizing her for her commitment to supporting the Foundation in our mission to advance PD therapies. Dr. Johnston is a leader in understanding the Parkin protein and its potential as a drug target, and her lab has provided critical insights and tools for the field.

We believe that genetic therapies offer great potential for PD, bringing much-needed therapeutic diversity to the PD pipeline. A Parkin gene therapy approach could not only impact people with genetic mutations in Parkin but may also be relevant to some subgroups with sporadic forms of PD. With still no disease-modifying therapy available for PD, moving a Parkin-directed therapy towards clinical testing would offer another critical and potentially promising advance for our community.

Sincerely,

Brian Fiske, PhD
Co-Chief Scientific Officer
The Michael J. Fox Foundation for Parkinson's Research