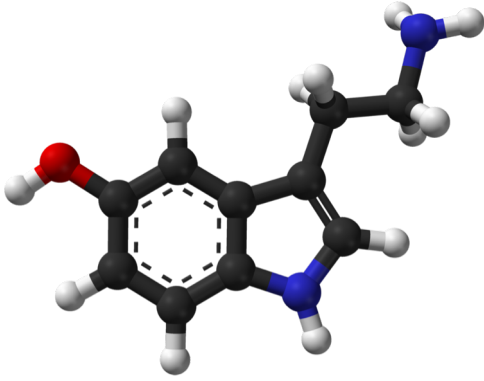
Appel

CONTENTS



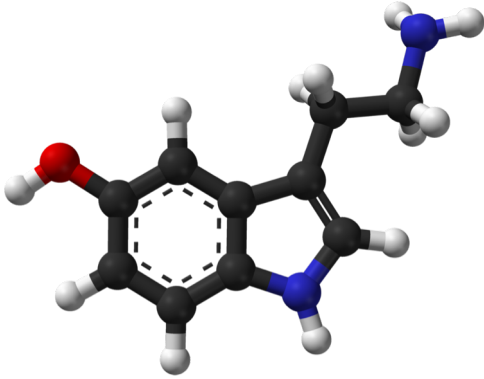
Vol. 4

Interview

Dr. Subhash Sinha
Associate Professor
of Research in Neuroscience
sus2044@med.cornell.edu

Subhash, who inspired you in your career to get to where you are today? Can you name that person and tell us how she or he inspired you?

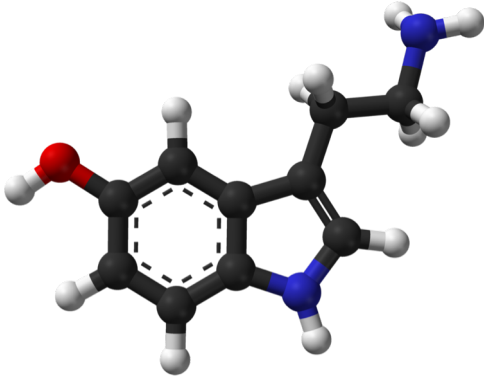
***S**urely, I appreciate and am thankful to Dr. Ehud Keinan, Dr. Richard A. Lerner, and Dr. K. Barry Sharpless for their support and giving me inspiration in many ways. I worked and collaborated with Dr. Keinan for nearly 2 decades (1989-2007), first couple years at Technion and later at the Scripps Research Institute, and with Dr. Lerner at Scripps for 14 years (1998-2012). I am also thankful to them for providing the letters of references.*



You are one of the inventors of the Aldolase antibody-chemical programming technology that led to an establishment of the CovX pharmaceuticals later bought by Pfizer, can you briefly describe your participation on this achievement?

***I** am one of 4 inventors listed in IP describing the aldolase antibody-chemical programming technology that combines small molecules with aldolase antibody to reprogram the latter to bind a target of the small molecule used. I, as a chemist, and Dr. Christoph Rader, a molecular biologist and biochemist, then both of us worked and collaborated together at the Scripps Research Institute, La Jolla, where we discovered this technology. The origin of this invention rests upon the discovery and development, by Dr. Richard A. Lerner and (Late) Dr. Carlos Barbas, of aldolase antibody using the reactive immunization technology. Specifically, immunization with a diketone hapten yielded aldolase antibodies that possessed reactive lysine residues in antibody binding sites. We used these antibodies and reacted with small molecule inhibitors of Integrin alpha(v)beta(3) to produce first chemically programmed antibody listed in our IP.*

Interview



You did your postdoctoral training in Tohoku University and Israel institute of Technology; can you share with us what was your experience in both places? Can you give any advice to our postdocs in Appel willing to continue their training in another university or country?

***Y**es, I was offered a postdoctoral fellowship from Tohoku University and a few weeks later from Technion-Israel Institute of Technology, but I had already accepted to join Tohoku by then. I went to Japan through Monbusho fellowship program. At Tohoku University, I worked with (Late) Professor Akira Yoshikoshi. My immediate supervisor was Dr. Fusao Kido, then an Assistant Professor. It was an interesting journey. For my Ph.D., I worked on plant chemistry-compounds isolation and structure determination, and I started postdoctoral training in synthetic chemistry and method development. Contrary to my expectation, this transition didn't prove very difficult. Life in Japan was very smooth and safe. I became quite habituated of working nearly 12 hours a day/7 days a week. In retrospect, I am happy that I had my first postdoctoral training in Japan and I am very thankful to Dr. Kido for providing his constant support. This proved very helpful in Israel and shaped my future career. Dr. Keinan had already offered me postdoctoral position prior to going to Japan, but he renewed the offer after my tenure in Japan. We collaborated and worked together for many years. Life in Israel was going fine until the Gulf war "Desert Storm" broke out in early 1991. Of course, due to the language barrier, we had some funny episodes both in Japan and in Israel, especially in Marketplace, but was manageable. My advice to postdocs willing to continue training in other laboratory and country is that he/she should utilize the opportunity and make out the best one can – every laboratory has something unique to offer.*

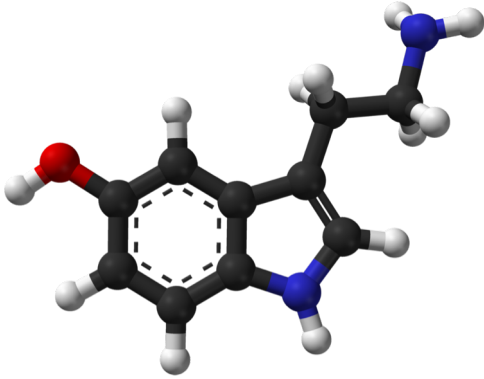
From your perspective, what is the most important discovery in Chemistry of all time?

***T**here have been numerous discoveries made in Chemistry and each discovery surely changed the world thereafter. Many discoveries in Physics and medicines also have a Chemistry basis. I consider Smallpox vaccine and Penicillin the two most important discovery in Chemistry or those with the Chemistry basis of all time. The concept of smallpox vaccine, and so to the many vaccines of current time, was laid well before oxygen was discovered in the late 18th century or the periodic table in early 19th century. However, the smallpox vaccine can be considered to have only a Chemistry basis, while Penicillin is indeed a chemical and antibiotic that saved many lives.*

What is your favorite musician and why?

***I** have primarily enjoyed hearing hindi songs especially when I was growing up and in my young age. There are many musicians to name, but one that is fresh in mind is AR Rahman. He brought the change to hindi music by giving new and unique tunes never heard before.*

Interview



What is your favorite book and why?

***W**hile textbooks and journals describing science that we perform every day in our life, Mahabharata is one other book very close to my heart. The contents are eternal truth and fresh in everyday life too. Although, Mahabharata is considered a religious book for Hindus, teachings presented are so true for everyone to practice in life.*

Can you share with us your future projects in Alzheimer's disease?

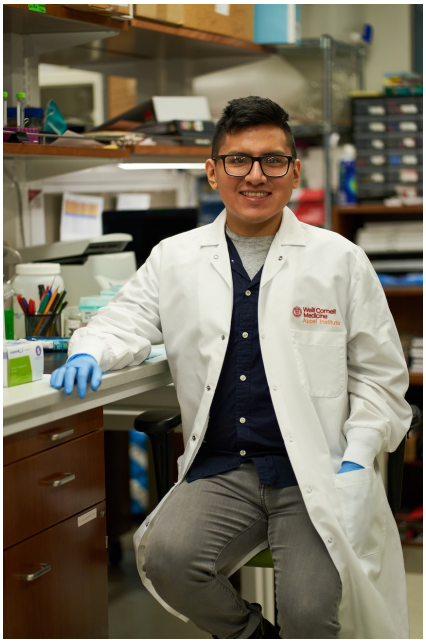
***W**e are working on multiple drug discovery projects that will have direct application in Alzheimer's disease. These are all collaborative projects with other PIs, including Li Gan and Anna Orr/Adam Orr laboratories, at Helen and Robert Appel Alzheimer's Disease Research Institute. The majority of our projects aim to develop modulators of microglial targets.*

Finally, can you share any advice to those who would like to pursue a career in Neuroscience?

***I** think that the individuals interested in pursuing career in Neuroscience need to keep eye wide open while performing their tasks as many discoveries have been made through 'Serendipity'. One should note and learn from both negative and positive results. Finally, a neuroscientist should not only pay attention to various cell types, receptors, transmitters, etc., in brain, but also to peripheral, including gut connections that appear to influence many neurodegenerative diseases.*

By **Guillermo Coronas**
Laboratory Manager
Appel Institute
guc9014@med.cornell.edu

Staff Highlights

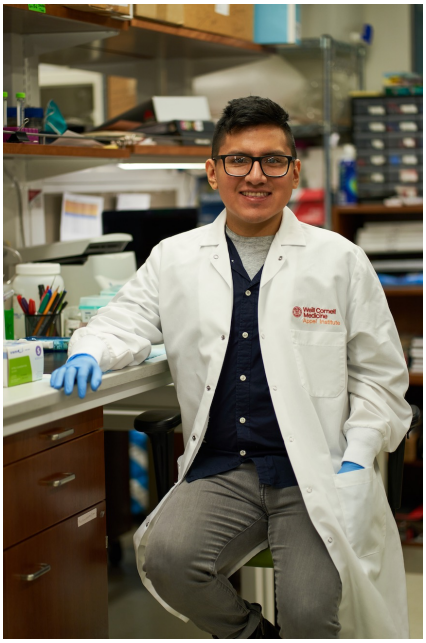


Fernando Palaguachi
Research Technician
Appel Institute
fep2005@med.cornell.edu

As an adolescent, I habitually had lucid dreams where I would wake up in an artificial world that my brain had conjured. These dreams were set in different cities that I would try to explore and interact with, before abruptly waking up. Ultimately, these subconscious experiences sparked my interest in how the brain functions. It wasn't until my early undergraduate career at SUNY Geneseo that I began to formally explore the field of neuroscience. My first psychology course touched upon different introductory subjects related to neuroscience, such as the anatomy and function of the brain, sensation and perception, and neuronal function. These topics generated more questions about the field and left me craving more depth. Geneseo unfortunately lacked a neuroscience department, and after that semester had concluded I was certain that I wanted to continue to explore and discover neuroscience.

Transferring schools is never easy. It means leaving behind an academic setting that you called home and saying goodbye to blossoming friendships. However, I knew that transferring to CUNY Queens College was a necessary step for my academic and early scientific growth. Once accepted into the Neuroscience undergraduate program, I was welcomed into a rich educational environment with abundant opportunities. At CUNY, I was able to explore different neuroscience courses and most importantly conduct scientific research. I joined Dr. Joshua Brumberg's laboratory to study neuronal circuitry in the mouse somatosensory cortex. The transition from lectures about the central nervous system to actively discovering knowledge through research was thrilling and momentous. In Dr. Brumberg's laboratory, I experienced a noteworthy list of small and simple firsts that laid the foundation for my research career. As I became familiarized with the lab's methodology and research, I felt optimistic about continuing a career in neuroscience research.

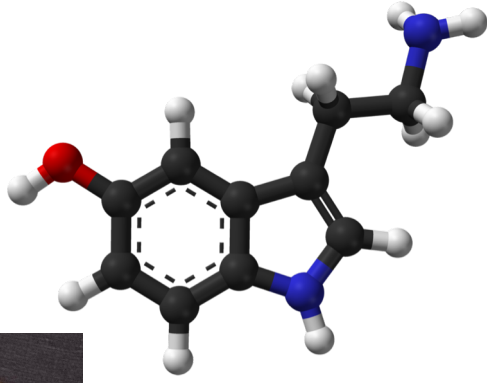
Staff Highlights



Fernando Palaguachi
Research Technician
Appel Institute
fep2005@med.cornell.edu

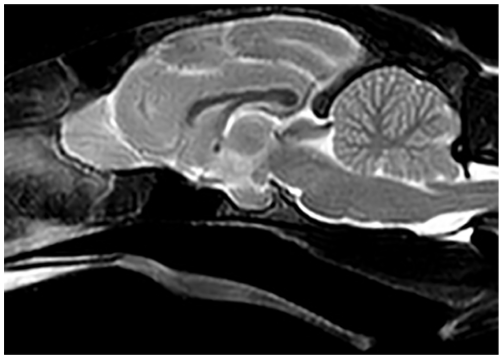
Shortly after graduating, I was certain about two things: continuing to grow as a researcher and learn more about CNS disorders. During the later years of my undergraduate experience, I attended lectures that covered different types of neurodegenerative disorders. I found the talks on Alzheimer's disease especially captivating since I found it difficult to comprehend how a world without memories could be possible. This, among other academic interests, would influence my decision to join the Orr laboratory as a technician. Throughout my tenure in the Orr Lab, I have been able to continue my pursuit of scientific knowledge, while also expanding my skill set. Working with the Orr lab has been an absolute pleasure. With their help and guidance, I have found myself growing as a scientist. My future aspiration is to pursuit a doctorate degree in neuroscience. Chiefly I am interested in studying the role of socioeconomic status and hippocampal development in migrant communities of color.

Meet Bubba

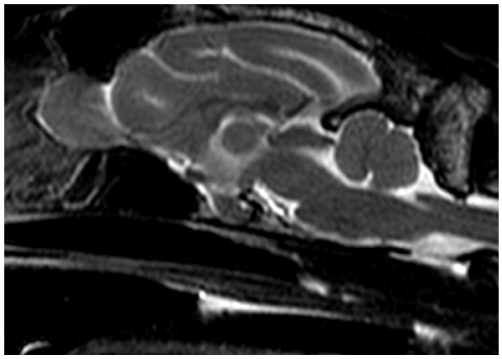


Bubba was found by Animal Care and Control as a small kitten. ASPCA pulled him off their euthanize list and brought him to their no-kill shelter, where I found him a few months later, at 4-months-old.

Bubba has cerebellar hypoplasia, so his cerebellum has been undeveloped since birth, making him very clumsy. He can't run or jump, but he can walk fairly well and uses his claws to climb up onto furniture.



Normal cat brain



Bubba's brain

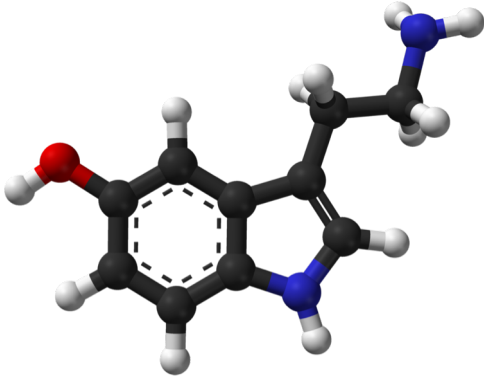
When I found Bubba, I was in college studying Neuroscience. I immediately thought he was a good fit for me because I could understand his neurological condition better than other people might.

Bubba is a really special cat, and I am very lucky to have him. He is now almost 5-years-old, and he brightens my life every day.

For more information about Bubba and his condition, see the article (and video!) written about him by the ASPCA after his adoption: https://www.aspca.org/news/disabled-kitten-finds-his-footing-perfect-adopters

Gillian Carling
Graduate Student
Appel Institute
gkc4001@med.cornell.edu

Poems



4/24/2021, in the park

Do you see my eager eyes
Wishing I could join you,
Wondering how it is
People form a group?

As I walk by I hear your music.

Bubblebath

You have to be able to sink
To feel like you're floating

4/23/2021

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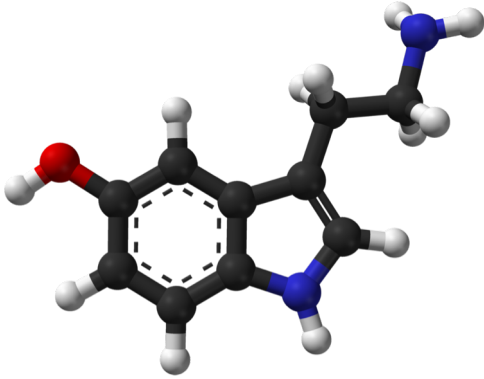
16 March 2021

I heard an airplane
And looked up and saw a bird.

(John Finley Walk, FDR, East River)

Silvie H Lundgren
Research Technician
Appel Institute
shl4016@med.cornell.edu

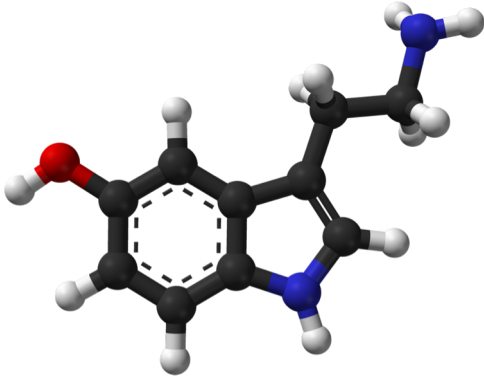
Welcome to Appel



Caitlin Castagnola
Graduate Student
Rotation Gan Lab
cmc4004@med.cornell.edu

Caitlin received her bachelor's in Neuroscience and Psychology from Boston University in 2017. After graduating, she joined Dr. Marc Tessier-Lavigne's lab at Stanford University as a research assistant studying activity-dependent structural plasticity of thalamocortical axons in the adult mouse barrel cortex. Along the way, she became increasingly interested in the interactions between neurons and non-neuronal cells, particularly in the context of neuroinflammation. In the Gan lab, she hopes to explore the relationship between microglia and neurons in Alzheimer's disease. When she's not in the lab, she probably has her head in a Terry Pratchett book while she patiently waits for in-person concerts to start up again.

Welcome to Appel

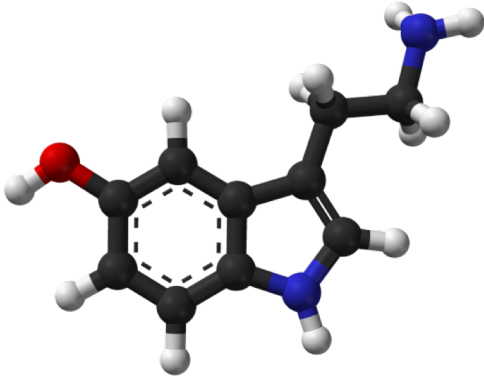


Connie Zhou received their Bachelor's degree in Molecular and Cellular Biology from Harvard University, with a secondary in Women and Gender Studies. During undergraduate training, Connie worked in the laboratory of Dr. Tracy Young-Pearse studying differential susceptibility of regional cell types to Alzheimer's disease pathogenesis using iPSC-derived neurons and astrocytes. For this work, Connie was awarded the Thomas Temple Hoopes prize and the Herchel Smith Undergraduate Research Fellowship. In the Orr lab, Connie is investigating the roles of TDP-43 in disrupting nucleocytoplasmic transport and other crimes of aberrant TDP-43. Outside of the lab, Connie is an avid Upper East Side cat parent and will show unsolicited pictures of their cat, Mimi!

Constance Zhou
MD-PhD student in the Weill Cornell/Rockefeller/Sloan Kettering Tri-Program
Orr Lab
coz2002@med.cornell.edu

News

Orr Lab



Anna Orr received the 2021 Weill Cornell Graduate School Neuroscience **Teaching and Mentoring Award**.

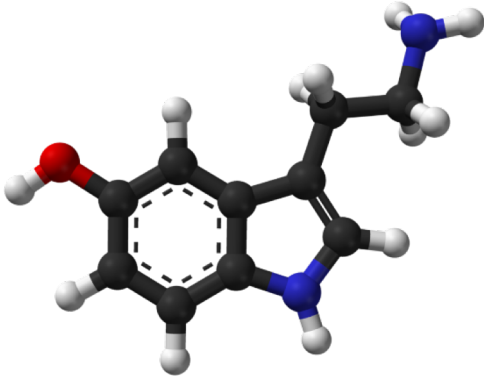
Constance Zhou formally **joined the Orr lab** for the PhD portion of the Tri-I MD-PhD program, and will be focusing on the roles of TDP-43 in glial-neuronal interactions.

Weill Cornell Medicine
BioPharma Alliances
& Research Collaborations

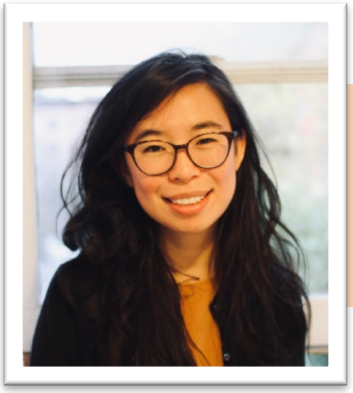
Adam Orr, Anna Orr, and Subhash Sinha received **funding from the Daedalus Fund for Innovation**, which is managed by the WCM BioPharma Alliances and Research Collaborations to advance early-stage translational projects toward successful industry partnerships.

News

Burré Lab



For her outstanding and meticulous scientific work, **Yoonmi Na** has been promoted from Research Specialist to Research Associate.

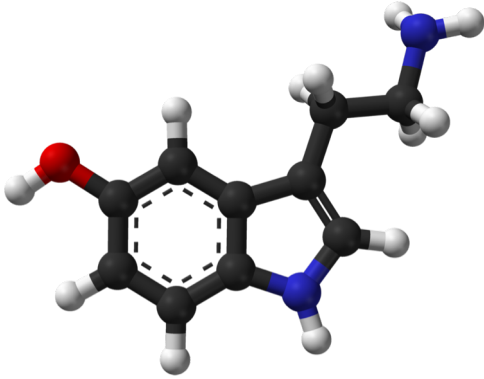


For her exemplary clinical service, **Virginia Gao** has been promoted to Chief Resident in the Dpt. of Neurology.

Jacqueline receives R01 funding for her work with **Dr. Jiajie Diao** at the University of Cincinnati on understanding the role of VAMP2 in alpha-synuclein function and pathology.

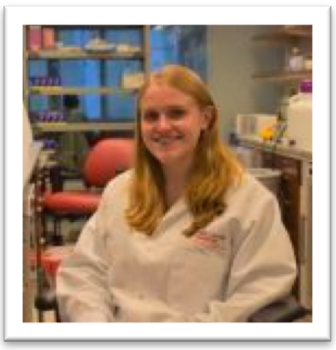
News

Gan Lab



Congratulations to **Chloe** for receiving **an NIH F31 award** for her project investigating how microglia contribute to sex-specific neuroinflammation in AD

Gloria and **Gillian** passed their **ACE exams** in April



Recent Publications

Gan Lab

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-22501-9 OPEN

Acetylated tau inhibits chaperone-mediated autophagy and promotes tau pathology propagation in mice

Benjamin Caballero[1,2,11,14], Mathieu Bourdenx[1,2,12,14], Enrique Luengo[1,2,3,4], Antonio Diaz[1,2], Peter Dongmin Sohn[5], Xu Chen[5], Chao Wang[5], Yves R. Juste[1,2], Susanne Wegmann[6,7], Bindi Patel[1,2], Zapporah T. Young[8], Szu Yu Kuo[8], Jose Antonio Rodriguez-Navarro[1,2,13], Hao Shao[8], Manuela G. Lopez[3,4], Celeste M. Karch[9], Alison M. Goate[10], Jason E. Gestwicki[8], Bradley T. Hyman[6], Li Gan[5] & Ana Maria Cuervo[1,2]✉

Disrupted homeostasis of the microtubule binding protein tau is a shared feature of a set of neurodegenerative disorders known as tauopathies. Acetylation of soluble tau is an early pathological event in neurodegeneration. In this work, we find that a large fraction of neuronal tau is degraded by chaperone-mediated autophagy (CMA) whereas, upon acetylation, tau is preferentially degraded by macroautophagy and endosomal microautophagy. Rerouting of acetylated tau to these other autophagic pathways originates, in part, from the inhibitory effect that acetylated tau exerts on CMA and results in its extracellular release. In fact, experimental blockage of CMA enhances cell-to-cell propagation of pathogenic tau in a mouse model of tauopathy. Furthermore, analysis of lysosomes isolated from brains of patients with tauopathies demonstrates similar molecular mechanisms leading to CMA dysfunction. This study reveals that CMA failure in tauopathy brains alters tau homeostasis and could contribute to aggravate disease progression

Recent Publications

Gan Lab

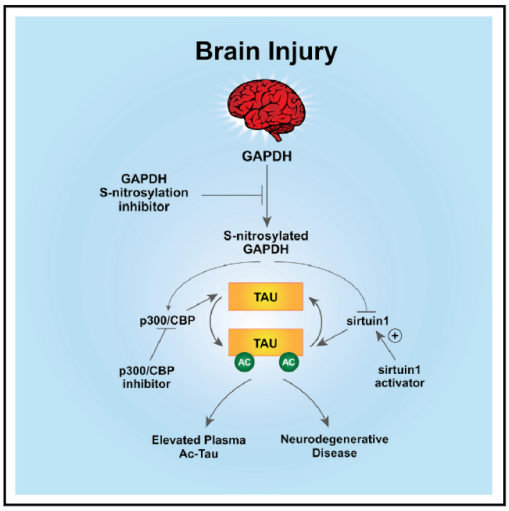
Cell

CellPress

Article

Reducing acetylated tau is neuroprotective in brain injury

Min-Kyoo Shin,[1,2,3,4,31] Edwin Vázquez-Rosa,[1,2,3,4,31] Yeojung Koh,[1,2,3,4] Matasha Dhar,[1,2,3,4] Kalyani Chaubey,[1,2,3,4] Coral J. Cintrón-Pérez,[1,2,3,4] Sarah Barker,[1,2,3,4] Emiko Miller,[1,2,3,4] Kathryn Franke,[1,2,3,4] Maria F. Noterman,[5] Divya Seth,[4,6] Rachael S. Allen,[7,8] Cara T. Motz,[7,8] Sriganesh Ramachandra Rao,[9,10] Lara A. Skelton,[9,10] Machelle T. Pardue,[7,8] Steven J. Fliesler,[9,10] Chao Wang,[11] Tara E. Tracy,[12] Li Gan,[13] Daniel J. Liebl,[14] Jude P.J. Savarraj,[15]



Traumatic brain injury (TBI) is the largest non-genetic, non-aging related risk factor for Alzheimer's disease (AD). We report here that TBI induces tau acetylation (ac-tau) at sites acetylated also in human AD brain. This is mediated by S-nitrosylated-GAPDH, which simultaneously inactivates Sirtuin1 deacetylase and activates p300/CBP acetyltransferase, increasing neuronal ac-tau. Subsequent tau mislocalization causes neurodegeneration and neurobehavioral impairment, and ac-tau accumulates in the blood. Blocking GAPDH S-nitrosylation, inhibiting p300/CBP, or stimulating Sirtuin1 all protect mice from neurodegeneration, neurobehavioral impairment, and blood and brain accumulation of ac-tau after TBI. Ac-tau is thus a therapeutic target and potential blood biomarker of TBI that may represent pathologic convergence between TBI and AD. Increased ac-tau in human AD brain is further augmented in AD patients with history of TBI, and patients receiving the p300/CBP inhibitors salsalate or diflunisal exhibit decreased incidence of AD and clinically diagnosed TBI.

Birthdays

May

16th Yoonmi

20th Bang

20th Noah

27th Ying

June

5th Marcella

Safety recommendations

Clean your hands often

Put distance between yourself and other people (at least 6 feet)

Cover your mouth and nose with a mask when around others

Clean and disinfect frequently touched objects and surfaces daily

Collaborations

Would you like to recommend a book, a movie or an inspiring quote?

You can participate!

Contact Billy for details: guc9014@med.cornell.edu