CURRICULUM VITAE

Samuel Matthew Young, Jr. PhD Dept of Anatomy and Cell Biology University of Iowa 51 Newton Rd Iowa City, IA 52242 Email Address: samuel-m-young@uiowa.edu

I. EDUCATIONAL AND PROFESSIONAL HISTORY

A. INSTITUTIONS ATTENDED

- 9/1992-6-1996 A.B. Molecular Biology Princeton University Princeton, NJ Senior Thesis 1995-1996 p53: Cell Cycle Control under direction of Arnold J. Levine, PhD
 8/96-5/2000 PhD. Genetics and Molecular Biology
- 8/96-5/2000 PhD. Genetics and Molecular Biology University of North Carolina-Chapel Hill Chapel Hill, NC Characterization of Adeno-Associated Virus Type 2 (AAV-2) Site-Specific Recombination Under direction of Richard Jude Samulski, PhD.

B. POSITIONS HELD

5/2000-7/2000	postdoctoral work Development of Purification for clinical grade recombinant AAV Vectors Under direction of Richard Jude Samulski, PhD
8/2000-11/2004	Research Associate (postdoctoral) Mechanisms of synaptic vesicle release and fusion in Hippocampal pyramidal neurons
	Development of viral vectors for neuronal transduction Under direction of Charles F. Stevens, MD, PhD. Salk Institute and Howard Hughes Medical Institute
11/2004-5/2009	Research Associate (postdoctoral) Molecular Mechanisms of synaptic transmission and plasticity at the Calyx of Held Under direction of Erwin Neher, PhD Dept of Membrane Biophysics Max Planck Institute for Biophysical Chemistry
6/2009-3/2010	Internal Research Group Leader Dept of Membrane Biophysics Max Planck Institute for Biophysical Chemistry

4/2010-11/2014	Independent Max Planck Research Group Leader (equivalent to Assistant Professor) Research Group Molecular Mechanisms of Synaptic Function Max Planck Florida Institute for Neuroscience
12/2014-5/2017	Max Planck Research Group Leader contract extension award (equivalent to Associate Professor) Independent Max Planck Research Group Leader Research Group Molecular Mechanisms of Synaptic Function Max Planck Florida Institute for Neuroscience
9/2010-5/2017	Affiliate Faculty-Florida Atlantic University Dept of Biological Sciences
9/2010-2/2017	Adjunct Faculty-The Scripps Research Institute Scripps Florida Neuroscience Department
6/2017-6/30/2022	Associate Professor (tenure) (Primary) Department of Anatomy and Cell Biology Associate Professor (tenure) (Secondary) Department of Otolaryngology Carver College of Medicine University of Iowa
7/2022-	Professor (tenure) (Primary) Department of Anatomy and Cell Biology Professor (tenure) (Secondary) Department of Otolaryngology Carver College of Medicine University of Iowa
6/2017-present	Director of Molecular Auditory Sciences Department of Otolaryngology
6/2017-present	Member, Iowa Neuroscience Institute
6/2017-present	Member, Pappajohn Biomedical Institute
7/2019-present	Program Director, Program in Gene and Cell Therapies for Auditory Disorders Carver College of Medicine, University of Iowa
11/2021-present	Vice Chair for Research Department of Anatomy and Cell Biology

C. HONORS AND AWARDS

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) "Molecular
Award FASEB

2016	Congressional Award Ceremony Keynote Speaker-18 th District Florida
2016	Individual Citation in US Congressional Record
2020	Iowa Distinguished Scholar Award

D. LEADERSHIP TRAINING

UI Lead Intercollegiate Leadership Program Summer 2022 Culturally Aware Mentorship Worshop, Mar 24 2022, Mar 31 2022

II. TEACHING ACTIVITIES

A. TEACHING ASSIGNMENTS

Instructor Flash photolysis course, November 2007, Goettingen

Co-developed and co-taught an electrophysiology lab course at Florida Atlantic University that was offered in 2012 and 2013, Advanced Neurophysiology Lab - BSC 6936 010.

Carnegie Mellon University- Cellular and Molecular Neuroscience Spring 2014 Lecture Feb 18, 2014. Presynaptic Release

Lecturer- Ultrafast and temporally precise information processing: Normal and Dysfunctional Hearing Methods Workshop "Targeted protein expression and conditional gene deletion in the auditory system" EPFL, Lausanne, Switzerland, (Nov 30 – Dec 3, 2014)

University of Iowa

Fundamental Neuroscience (BIOL5633) Fall 2017, Fall 2018, Fall 2020, Fall 2021 pending Lecturer, Peripheral Auditory Transduction lecture

Critical Thinking in Molecular Medicine (MMED:6280) Spring 2019 Course Instructor

Critical Thinking in Biochemistry and Molecular Biology (CDB:6237) Fall 2019, 2020,2021 pending Course Instructor

Biomedical Science Seminar (BMED:7777) Fall 2021 pending Lecturer

B. Students, Postdoctoral Fellows, Medical Fellows and Research Scientists Supervised

Post doctoral

Monica Montesinos, PhD	7/2009-6/2016	postdoctoral advisor
Wei Dong, PhD	3/2013-5/2017	postdoctoral advisor
Matthias Luebbert, PhD	2/2014-6/2017	postdoctoral advisor
Rene Oliver Goral, PhD	4/2015-9/2018	postdoctoral advisor
Christian Keine, PhD	3/2017-6/2020	postdoctoral advisor
Tamara Radulovic, PhD	3/2017-6/2020	postdoctoral advisor
Stacia Phillips-Ormsby, PhD	6/2017-3/2021	res. scientist advisor

Priyadharishini Veeraraghavan, PhD Mohammed Al-Yaari, PhD Emre Kul, PhD Neda Mokhberian, PhD		7/2017-7/31/2022 11/2021-present 12/2021-present 1/2023-present	postdoctoral advisor postdoctoral advisor postdoctoral advisor postdoctoral advisor
Medical Fellows Tatiana Correa. MD (Otolaryngology) Osama Tarabichi, MD (Otolaryngology)		8/2019-present 8/2020-prsent	co-mentor with Marlan Hansen, MD co-mentor with Marlan Hansen,MD
PhD students Zuxin Chen	12/2008-12/2013		warded by hD studies carried out
Brati Das	8/1/2011-5/2016	in my laboratory) PhD. Advisor Florida Atlantic University IBAN program PhD, exchange student, Kurume University, Japan	
Satoko Okayama	7/2016-7/2017		
Iva Macova	7/2018-12/2018	PhD, exchange stude Institute of Biotechno Czech Rebpublic	
Jianing Li	8/2019-present	PhD advisor	ell Develop Bio program
William Milanick	6/2020-present	PhD advisor	euroscience program
Madhuri Bendale	2/2022-present	PhD advisor	ell Develop Bio program
Uchechi Okoroafor	6/2022-present	PhD advisor	ell Develop Bio program
YunWen "Wendy" Xu	I 6/2023-present	PhD advisor University of Iowa- C	ell Develop Bio program

PhD rotation students University of Iowa

Sydney Houlton	Fall 2018	Neuroscience PhD program
Kara Misel	Fall 2018	Molecular Medicine PhD program
Cody Poe	Fall 2019	Molecular Medicine Program
Jianing Li	Fall 2019	Cell Develop Bio PhD program (direct admit)
William Milanick	Winter 2019/2020	Neuroscience PhD program
Ahmet Kuraly	Fall 2020	Neuroscience PhD program
Ashby Martin	Fall 2021	Neuroscience PhD program
Madhuri Bendale	Fall/Winter2021/2022	Biomedical Science Program
Uchechi Okoroafor	Spring 2022	Biomedical Science Program
Andrew G Kain	Fall 2022	Neuroscience PhD program
Wendy Xu	Fall/Winter2022/2023	Biomedical Science Program

Undergraduate students

Aniela Murphy	6/2016-5/2017	MPFI Scholars Program Florida Atlantic University
Danick Joseph	6/2015-6/2016	MPFI Scholars Program Florida Atlantic University
Johanna Mucke	9/1/2011-1/2012	Medical Thesis Advisor University of Heidelberg, Germany
Kelly Hildebrandt	8/2012-12/2013	Undergraduate Honors Thesis Florida Atlantic University
Lauren Dahl	9/2017- 6/2018	University of Iowa
Dani Todd	9/2018-4/2019	University of Iowa
Brynn K. Helm	2/2019-4/2020	University of Iowa
Ryan Sabotin	6/2019-8/2019	University of Iowa
Lindsey Katschmitter	8/2019-3/2020	University of Iowa
Lauren Palkovic	3/2021-6/2022	University of Iowa
Amanda Dougherty	3/2021-6/2022	University of Iowa
Windy Ngyuen	6/2021-12/2022	University of Iowa
Leah Aberman	10/2021-present	University of Iowa
Bella Cesarz	10/2021-10/2022	University of Iowa
Ryan Byrd	1/2023-present	University of Iowa
Amanda Zumbrock	6/2023-8/2023	Iowa State University (UI SROP)

Post baccalaureate students

Kevin Goff	6/2014/-6/2015
Avalokiteswari Kurup	11/2014-7/2015
Travis Putzke	6/2015-1/2017
Paula Valino Ramos	7/2020-present

C. Other Contributions to Institutional Programs

Graduate Program Committees

Max Planck Florida Institute for Neuroscience

Helped Establish FAU/MPFI collaboration which resulted in FAU IBAN program 2010-2011

FAU IBAN Graduate Admissions Committee in 2011

Max Planck Florida Institute for Neuroscience International Max Planck Research School Steering Committee Member 1/2015-2017

University of Iowa

University of Iowa Molecular Medicine PhD admissions committee 2018/2019 University of Iowa Neuroscience PhD admissions committee 2018-2021 University of Iowa Carver College of Medicine Medical Scientist Training program admissions committee 2020-2021

University of Iowa- Dept of Otolaryngology

University of Iowa Dept of Otolaryngology Resident Fellow admissions 2017-present

Masters Committees

University of Iowa

Nora N Bensellam, Master of Clinical Anatomy Program

PhD Committees

University of Iowa

Benjamin Gansemer-iBio PhD programNoah Armstrong-
Jianing LiNeuroscience PhD programOnnique Weaver
William MilanickCell and Developmental Biology PhD programWilliam Milanick
Maria WongNeuroscience PhD programAhmad Al SanehMolecular Physiology and Biophysics PhD program

Florida Atlantic University

Brati Das- IBAN PhD program

External PhD Committees

Chong Chen – IST Austria-Peter Jonas PhD advisor Enmanuel Perez – University of Miami- Daniel J. Liebl PhD advisor Lee Lesperance – University of Toronto- Lu-Yang Wang PhD advisor Cristina Matthewman –University of Miaimi- Laura Bianchi PhD advisor Andrea Nicole Gensky- Oklahoma State University Liz McCullagh PhD advisor

III. SCHOLARSHIP/PROFESSSIONAL PRODUCTIVITY

A. PUBLICATIONS

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/samuel.young.1/bibliography/public/ Publications

Color Key:

gray = undergraduate; orange = graduate student; purple = postdoctoral trainee; blue = faculty member

Code Key:

a: Major responsible author as trainee: conceived, directed, analyzed, and documented the investigation under faculty supervision.

b: Major responsible (first) author as faculty member: conceived, directed, analyzed,

documented the investigation, and served as corresponding author.

c: Senior author: served as corresponding author; supervised major responsible author, who was usually a trainee.

d: Co-author (as trainee or faculty): contributed to conception, conduct, analysis, and/or documentation, but not major responsible author.

1. Notterman, D., Young, S.M. Jr (d)., Wainger, B., Levine, A.J. Prevention of mammalian DNA reduplication, following the release from the mitotic spindle checkpoint, requires p53 protein, but not p53-mediated transcriptional activity. Oncogene. 17, 2743-2751. (1998)

2. Gavin, D.K. Young, S.M.Jr (d)., Xiao, W., Temple B., Abernathy., C.R. Peraira, D.J., Muzyczka, N., and Samulski, R.J. Charge-to-Alanine Mutagenesis of Adeno-associated Virus Type 2 Rep78/68 proteins yields temperature-sensitive and magnesium-dependent variants. Journal of Virolog. 73(11)9433-9445. (1999)

3. Young, S.M. Jr.(a), Xiao, W., and Samulski, R.J. Site specific targeting of DNA plasmids to chromosome 19 using AAV Cis and Trans sequences. Gene Targeting Vector Protocols Methods in Molecular Biology, Editor. E.B. Kmiec, Humana Press, Totowa, NJ, 2000.

Methods in Molecular Biology. 133:111-26. (2000)

4. Young, S.M. Jr. (a), McCarty, D.M., Natalya Degtyareva, and Samulski, R.J. Roles of Adeno-Associated Virus Rep Protein and Human Chromosome 19 in Site-Specific Recombination. Journal of Virology. 74(9)3953-3966. (2000)

5. Young, S.M. Jr. (a), and Samulski, R.J. Adeno-associated virus (AAV) site-specific recombination does not require a Rep-depedent origin of replication within the AAV terminal repeat. PNAS. 98(24), 13525-13530. (2001)

Cited for outstanding discoveries in Discovery Medicine 1(2)

6. Weitzman, M.D., Young, S.M. Jr (d)., Cathomen, T., and Samulski, R.J. Targeted integration by adeno-associated virus. Methods Mol Med. 76201-19. (2003)

7. McCarty, D.M., Young, S.M. Jr (a)., and Samulski, R.J. Integration of Adeno-Associated Virus. (invited) Annu Rev Genet. 38:819-45. (2004)

8. Young, S.M. Jr (a). Proteolysis of SNARE proteins alters facilitation and depression in a specific way. PNAS. 102(7):2614-9. (2005)

9. Schikorski, T., Young, S.M. Jr (d)., Hu, Y. Horseradish peroxidase cDNA as a marker for electron microscopy in neurons. J Neurosci Methods. 165(2):210-5. (2007)

10. Young, S.M. Jr. (a) and Neher, E. Synaptotagmin has an essential function in synaptic vesicle positioning for synchronous release in addition to its role as a calcium sensor. Neuron. 63(4):482-496. (2009)

11. Kawabe, H., Neeb, A., Dimova, K., Young, S.M. Jr (d), Takeda, M., Katsurabayashi, S., Mitkovski, M., Malakhova, O.A., Zhang, D., Umikawa, M., Kariya, K., Goebbels, S., Nave, K., Rosenmund, C., Jahn, O., Rhee, J.S., and Brose, N. Regulation of Rap2A by Nedd4-1 Controls Dendrite Development in Cortical Neurons. Neuron. 65(3):358-72. (2010)

12. Dusonchet, J. Kochubey O, Stafa K, Young, SM Jr.(d) Zufferey R. Moore DJ, Scheider BL, Aebischer P. A rat model of progressive nigral neurodegeneration induced by the Parkinson's disease-associated G2019S mutation in LRRK2. J. Neurosci 19;31(3):907-12. (2011)

13. Montesinos MS, Chen Z. Young, SM. Jr. (c) pUNISHER: A high level neuro-specific expression cassette for use with recombinant viral vectors for rapid and long term *in vivo* expression in the CNS. J Neurophysiol. 2011 Dec;106(6):3230-44

14. Chen, Z., Cooper, B., Kalla, S., Varoqueaux, F., Young, SM. Jr.(c) (2013) The Munc13 proteins differentially regulate readily releasable pool dynamics and calcium-dependent recovery at a central synapse. J Neurosci. 8;33(19):8336-8351

15. Tong, H., Kopp-Scheinpflug, C., Pilati, N., Robinson, S., Sinclair, J., Steinert, J., Barnes-Davies, M., Allfree, R., Grubb, B., Young, SM. Jr.(d), Forsythe, ID. (2013) Protection from noise-induced hearing loss by Kv2.2 potassium currents in the central medial olivocochlear system. J Neurosci. 22;33(21):9113-22

16. Maltecca, F., Bassegio, E., Consolato, F., Mazza, D., Podini, P., Young, SM. Jr.(d)., Drago, I., Bahr, B., Puliti, A., Codazzi, F., Quattrini, A., Casari G., (2015) Purkinje neuron Ca2+ influx

reduction rescues ataxia in SCA28 model. Journal of Clinical Investigation 125(1) 263-274

17. Chen, Z., Das B., Nakamura, Y., DiGregorio, D., **Young, SM. Jr.(c)** (2015) Ca²⁺ Channel to Synaptic Vesicle Distance Accounts for the Readily Releasable Pool Kinetics at a Functionally Mature Auditory Synapse J Neurosci. 35(5):2083-2100

18, Montesinos, M.S., Goff, K., Das, B., Guerro-Givens, D., Dong, W. Schmalzigagu, RPremont, R.T., Kamasawa, N., Young, SM. Jr.(c) (2015) Presynaptic deletion of GIT proteins results in increased synaptic strength at a mammalian central synapse. Neuron 88, (5) 918-925

19. Montesinos, M.S., Richards, R., Young, SM. Jr.(c) (2016) Helper Dependent Adenoviral vectors and their use in neuroscience applications. High Resolution Imaging of Proteins in Tissues and Cells:Light and Electron Micrscopy Methods and Protocols: Editors Steven D. Schwartzbach, Omar Skalli, and Thomas Schikorski. Springer Press Vol 1474 pp73-92

20. Chen, C. Arai, I. Satterfield, R. Young, SM. Jr.(d)., Jonas, P. (2017) Synaptotagmin is the Fast Ca2+ sensor at a Central Inhibitory Synapse. Cell Reports 18, 723-736

21. Luebbert, M, Goral. R., Satterfield, R. Putzke, T. van den Maagedenburg, A, Kamaswa, N. Young, SM. Jr.(c) (2017) A novel region in the CaV2.1 α1 subunit C-terminus regulates fast vesicle fusion and vesicle docking at the mammalian presynaptic active zone. Elife. 2017 Aug 8;6. pii: e28412. doi: 10.7554/eLife.28412.

Selected by F1000 as special significance in the field.

22. Chen C, Satterfield R, Young, SM. Jr.(d), Jonas P (2017) Triple Function of Synaptotagmin 7 Ensures Efficiency of High-Frequency Transmission at Central GABAergic Synapses. Cell Rep. 2017 Nov 21;21(8):2082-2089

23.Sutton LP, Orlandi C, Song C, Oh WC, Muntean BS, Xie K, Filippini A, Xie X, Satterfield R, Yaeger JDW, Renner KJ, Young, SM. Jr.(d), Xu B, Kwon H, Martemyanov KA. Orphan receptor GPR158 controls stress-induced depression. Elife. 2018 Feb 8;7. pii: e33273. doi: 10.7554/eLife.33273.

24.Durán E, Montes MÁ, Jemal I, Satterfield R, Young S (d), Álvarez de Toledo G. (2018) Cell Calcium. Sep;74:53-60. doi: 10.1016/j.ceca.2018.06.004. Epub 2018 Jun 22.

25. Dong W, Radulovic T, Goral RO, Thomas C, Suarez Montesinos M, Guerrero-Given D, Hagiwara A, Putzke T, Hida Y, Abe M, Sakimura K, Kamasawa N, Ohtsuka T, Young, SM. Jr.(c). (2018) CAST/ELKS Proteins Control Voltage-Gated Ca₂₊ Channel Density and Synaptic Release Probability at a Mammalian Central Synapse. Cell Rep. Jul 10;24(2):284-293.e6. doi: 10.1016/j.celrep.2018.06.024.

26. Ostrovskaya OI, Orlandi C, Fajardo-Serrano A, Young, SM. Jr.(d), Lujan R, Martemyanov KA. (2018) Inhibitory Signaling to Ion Channels in Hippocampal Neurons Is Differentially Regulated by Alternative Macromolecular Complexes of RGS7. J Neurosci. Nov 14;38(46):10002-10015. doi: 10.1523/JNEUROSCI.1378-18.2018. Epub 2018 Oct 12.

27. Lübbert M, Goral RO, Keine C, Thomas C, Guerrero-Given D, Putzke T, Satterfield R, Kamasawa N, Young, SM. Jr.(c). (2019) Ca_V2.1 α_1 Subunit Expression Regulates Presynaptic

 $Ca_{v}2.1$ Abundance and Synaptic Strength at a Central Synapse. Neuron. 2019 Jan 16;101(2):260-273.e6. doi: 10.1016/j.neuron.2018.11.028. Epub 2018 Dec 10.

28. Thomas CI, Keine C, Okayama S, Satterfield R, Musgrove M, Guerrero-Given D, Kamasawa N, **Young, SM. Jr.(c)** (2019) Presynaptic Mitochondria Volume and Abundance Increase during Development of a High-Fidelity Synapse. J Neurosci. 2019 Oct 9;39(41):7994-8012. doi: 10.1523/JNEUROSCI.0363-19.2019. Epub 2019 Aug 27. PubMed PMID: 31455662; **Selected by F1000 as special significance in the field.**

29. Green MV, Pengo T, Raybuck JD, Naqvi T, McMullan HM, Hawkinson JE, Marron Fernandez de Velasco E, Muntean BS, Martemyanov KA, Satterfield R, Young, SM. Jr.(d), Thayer SA. Automated Live-Cell Imaging of Synapses in Rat and Human Neuronal Cultures Front Cell Neurosci. 2019 Oct 17;13:467. doi: 10.3389/fncel.2019.00467. eCollection 2019. PMID:31680875

30. Yamoah EN, Li M, Shah A, Elliott KL, Cheah K, Xu PX, Phillips S, Young, SM. Jr.(d), Eberl DF, Fritzsch B. (2020) Using Sox2 to alleviate the hallmarks of age-related hearing loss. Ageing Res Rev. 2020 May;59:101042. doi: 10.1016/j.arr.2020.101042. Epub 2020 Mar 12. Review. PMID:32173536

31. Radulovic T, Dong W, Goral RO, Thomas CI, Veeraraghavan P, Montesinos MS, Guerrero-Given D, Goff K, Lübbert M, Kamasawa N, Ohtsuka T, Young, SM. Jr.(c). (2020) Presynaptic development is controlled by the core active zone proteins CAST/ELKS. J Physiol. Apr 18. doi: 10.1113/JP279736. PMID:32304329 Selected by F1000 as special significance in the field.

32. Young, SM. Jr.(c). and Veeraraghavan P (2021) Presynaptic voltage-gated calcium channels in the auditory brainstem Mol Cell Neuro April 112 doi.org/10.1016/j.mcn.2021.103609

33. Phillips S, Valino-Ramos, P, Veeraraghavan, P, Young, SM. Jr.(c) VikAD, a Vika site-specific recombinase-based system for efficient and scalable helper dependent adenovirus production Molecular Therapy Methods and Clinical Development 8)

34. Keine C, Al-Yaari M, Radulovic T, Thomas CI, Valino Ramos P, Guerrero-Given D, Ranjan M, Taschenberger H, Kamasawa N, Young, SM. Jr.(c). Presynaptic Rac1 controls synaptic strength through the regulation of synaptic vesicle priming. Elife. 2022 Oct 10;11:e81505. doi: 10.7554/eLife.81505

35. Young, SM. Jr.(c). Centering on synaptic vesicle release. Cell Calcium. Cell Calcium. 2023 Jan;109:102686. doi: 10.1016/j.ceca.2022.102686. Epub 2022 Dec 11.

36. Tarabichi, O. Correa, T, Kul, E, Phillips, S, Darkazanly, B, Young, SM. Jr.(c), Hansen, MR. Development and evaluation of helper dependent adenoviral vectors for inner ear gene delivery. Hearing Research (*in press*)

37. Keine, C. Al-Yaari, M. Radulovic, T. Young, SM. Jr.(c). Stereotactic delivery of helperdependent adenoviral viral vectors at distinct developmental time points to perform age-dependent molecular manipulations of the mouse calyx of Held. Bio-protocol (in press)

38. Keine, C. Al-Yaari, M. Radulovic, T. Young, SM. Jr.(c). Confocal imaging and 3D reconstruction to determine how genetic perturbations impact presynaptic morphology at the mouse calyx of Held (in press)

Manuscripts under revision

Li, J. Veeraraghavan, P, Young, SM. Jr.(c) Ca_V2.1 α_1 subunit motifs that control presynaptic Ca_V2.1 subtype abundance are distinct from Ca_V2.1 preference Journal of Physiology (*under revision*)

Manuscripts in preparation

Kul, E, Okoroafor, U, **Young, SM. Jr.(c)** Viral vectors and their applications probing synaptic function (*Invited Review* to Journal of Physiology, planned submission 2/2023)

PATENTS

Phillips S., **Young, SM. Jr**. Novel Site-Specific Recombinase-Based Production System for Efficient and Scalable Production of Helper-Dependent Adenovirus (2022) **Provisional Patent filed by UIRF**)

Kul, E, Young, SM. Jr. CD46 binding vectors and uses therof to treat CNS disorders (2023) Provisional patent filed by UIRF)

PUBLICATIONS (Theses)

Young, SM Jr. p53: Cell Cycle Control, Undergraduate dissertation, Princeton University (1996)

Young, SM Jr. Characterization of Adeno-associated type 2 (AAV-2) Site-Specific Recombination, PhD. Dissertation, UNC-Chapel Hill. (2000)

B. AREAS OF RESEARCH INTEREST AND CURRENT PROJECTS

Synaptic Control of Auditory information processing

Fundamental to hearing is the ability to localize sound sources and detect temporal features of sound. An inability to do so results in problems with sound localization, speech perception, and in cognitive impairments. Sound information encoding within the initial auditory processing stations in the auditory brainstem requires reliable and precise synaptic transmission in response to rapid and large fluctuations in action potential (AP) firing rates to nearly one kHz. However, the molecular mechanisms in auditory brainstem synapses that control accurate identification and perception of sound are largely unsolved. To provide definitive answers about synaptic control of ultra-fast auditory information processing, we focus on the molecular mechanisms regulating presynaptic function at the calyx of Held/medial nucleus of the trapezoid body (MNTB) synapse; a critical synapse for encoding sound localization and temporal features of music and communication sounds. The calvx of Held is the sole input driving AP spiking in the MNTB, which in turn regulates key mono and binaural sound processing cell groups. It is an ideal model to elucidate how a single synapse controls auditory information processing. Utilizing our virology expertise, we created unique viral vector technologies and techniques that permitted routine molecular perturbations at the calyx of Held. By combining our molecular approaches with advanced biophysical, electrophysiological, imaging, and modeling approaches our goal is to delineate the molecular mechanisms regulating high-fidelity synaptic transmission at unprecedented resolution. Ultimately, we will build the framework of molecular principles for accurate sound information encoding and how they contribute to auditory deficits.

Current projects

<u>Regulation of Synaptic Vesicle Dynamics in the initial stages of auditory signaling.</u> The goal of this project is to delineate the molecular mechanisms that control the temporal dynamics of SV release and replenishment.

<u>Presynaptic regulation of voltage-gated Ca²⁺ channels.</u> The goal of this project is to reveal new molecular mechanisms that regulate Cav2.1 channel function at the synapse and their role in regulating synaptic transmission in neuronal circuits.

Elucidating the roles of $\alpha 2\delta$ protein family in regulation of mammalian synaptic function. The goal of this project is to is to establish how $\alpha 2\delta 2$ family regulate synaptic function and neuronal circuit output.

Viral Vector Mediated Gene Therapy Approaches for Hearing and Balance Disorders

While The goal is overcome the current hurdles in translational approaches to develop treatments for sensorineural hearing loss, vestibular hypofunction, cerebellar ataxia and neurodegeneration. My goal is to develop HdAd gene therapy approaches for specific classes of these disorders that are caused by mutations in genes that exceed the AAV packaging capacity. A genetic form of early onset hearing loss and vestibular hypofunction is due to loss of function mutations in the Otoferlin (*OTOF*) gene, which has a coding sequence of ~6 kb. Spinocerebellar Ataxia Type 6 (SCA6) and Ataxia-Telangiectasia (A-T) result in cerebellar ataxia and neurodegeneration that is largely due to loss of Purkinje cells, the sole output neurons of the cerebellar cortex. SCA6 is caused by toxic gain of function mutations in the *CACNA1A* gene, which has a coding sequence of 8.6 kb. A-T is due to loss of function mutations in *ATM* (<u>Ataxia-Telangiectasia Mutated</u>), which has a coding sequence of 9.5 kb. Since SCA6 are caused by dominant mutations, therapies will require not only delivery of the wild-type gene, but also silencing of the endogenous mutant protein.

Current projects

<u>Development of novel gene therapy strategies to treat CACNA1A disorders.</u> The goal is to develop novel viral vector gene therapy strategies that restore CACNA1A function to prevent cerebellar dysfunction in CACNA1A patients.

<u>Development of novel gene therapy stragies for treatment of all SCN2A Disorders</u> Our goal is to develop a viral vector gene therapy approach using helper-dependent adenovirus (HdAd) based delivery, which could be used to treat all forms of SCN2A Disorders

<u>Develop novel HdAd vectors with altered tropism and cell lines for their production</u>. Many neuronal cell-types that are lost in neurodegenerative diseases are refractory to Ad Type transduction. Our goal is to create novel Ad vectors with new tropism to preferentially transduce our cells of interest.. If possible, we intend to partner with a facility for screening in non-human primate.

<u>Develop novel genetic models for testing and validation of therapy.</u> Our goal is to use available or create new human stem cell models of *OTOF*, SCA6, SCN2A or A-T to develop transgene cassettes that can express the wild-type protein and silence the mutated gene. Since RNA interference been approved by the FDA (<u>www.fda.gov</u>), we will use these models to screen for effective shRNAs that result in >90% knockdown of the protein. We will also develop transgene cassettes for expression of wild-type protein at therapeutic levels.

PUBLISHED REVIEWS OF SCHOLARSHIP

Location matters: synaptotagmin helps place vesicle near calcium channels. McNeil BD, Wu LG.Neuron. 2009 Aug 27;63(4):419-21. doi: 10.1016/j.neuron.2009.08.001 Review of Young and Neher, 2009)

C. GRANTS RECEIVED **RESEARCH SUPPORT Ongoing**

R01 DC014093-07

National Institutes for Deafness and Communication Disorders

Regulation of Synaptic Vesicle Dynamics in the Auditory System

The goal of this project is to determine the molecular mechanisms that enable sound encoding in response to changes in firing rates through the dynamic range of amplitude and temporal (frequency) modulation.

PI: Young

R01 NS110742-01 12/1/2019-11/30/2024

Presynaptic regulation of neurotransmitter release in mammalian neuronal circuits The goal of this project is to reveal new molecular mechanisms that regulate Cav2.1 channel function at the synapse and their role in regulating synaptic transmission in neuronal circuits in the mammalian central nervous system PI:Young

R03TR004161-01

7/2022-7/2023

Elucidating the roles of CACNA2D2 and CACNA2D3 in presynaptic regulation of mammalian synaptic function

The goal of this project is to is to establish how $\alpha 2\delta 2$ and $\alpha 2\delta 3$ regulate synaptic function and neuronal circuit output. Despite being highly expressed throughout the central nervous system (CNS) and the clear linkage between human mutations in $\alpha 2\delta 2$ and $\alpha 2\delta 3$ and CNS disorders, very little is known about the roles of $\alpha 2\delta 2$ and $\alpha 2\delta 3$ in regulating synaptic function. Therefore, our findings will provide fundamental insights into how information is encoded by the CNS and will facilitate the development of treatments for a wide range of neurological disorders due to $\alpha 2\delta 2$ and $\alpha 2\delta 3$ mutations.

PI:Young

Orphan Disease Center 2022 Million Dollar Bike Ride

2/2023-2/2024 Development of novel gene therapy stragies for treatment of all SCN2A Disorders Our goal is to develop a viral vector gene therapy approach using helper-dependent adenovirus (HdAd) based delivery, which could be used to treat all forms of SCN2A Disorders.

Industry Partnership

7/2022-7/2024

Recombinant AAV capsid library screening to identify clinically relevant capsid variants in humans Our goal is to develop AAV vectors that will be relevant for use in humans Multi-PI (Young, Hansen (Dept of Otolaryngology), Howard (Dept of Neurosurgery).

CACNA1A Foundation

3/2023-3/30/2024

Development of novel gene therapy strategies to treat CACNA1A disorders. The goal is to develop novel viral vector gene therapy strategies that restore CACNA1A function to prevent cerebellar dysfunction in CACNA1A patients. PI:Young

NHLBI

3/1/2023-2/28/2028

Life-ling phenotypic Correction of CF Airways My goal in this project is to develop novel HdAd Vectors that can successfully transduce the airway in CF patients PI:Sinn - Co-PI Young

4/1/2015-6/30/2025

COMPLETED Research Support:

University or Iowa Distinguished Scholar Award

R21DC018242-01

PI: Young

National Institutes for Deafness and Communication Disorders Development of Helper Dependent Adenoviral Vectors for Inner Ear Gene Therapy **Approaches**

The goal of this project is to develop novel platform technology for viral vector-based gene therapy strategies to treat hearing loss.

Multiple PI (Young:PD/PI/Hansen PI)

R01 DC007695-10

(USF Subaward to University of Iowa)

Development of the Calyx of Held

The goal of this project will be to provide the first wholistic view of neural circuit development that incorporates all cell types and describes circuit formation from the time of initial contact at embryonic ages to mature topography by hearing onset during the second postnatal week. PI Spirou Co-PI: Young. Our role in the project was to supply viral vectors

R01 DC014093-06

National Institutes for Deafness and Communication Disorders

Regulation of Synaptic Vesicle Dynamics in the Auditory System

The goals of this project are to determine the molecular mechanisms that enable sound encoding in response to changes in firing rates through the dynamic range of amplitude and temporal (frequency) modulation.

PI: Young

Aging Mind Brain Initiative University of Iowa (Young:PI) 12/2017-6/2019 Helper Dependent Adenoviral Vectors for Gene Therapy Approaches for Age-Related Hearing Loss

As there are no known biological treatments for hearing restoration in the aging population, our objective is to bridge this gap by developing platform technology for viral vector-based gene therapy strategies to treat age-related hearing loss.

Michael J. Fox Foundation (Young: PI)

Production of HdAd Type 5 LRRK2 expression vectors

The goal of this project is to produce an HdAd LRRK2 expression vector that can be used by all Parkinson disease researchers. By creating a HdAd viral vector that expresses LRRK2 and its dominant negatives this will allow researchers to use this viral vector to help elucidate the mechanisms of LRRK2 function in vivo and design relevant therapeutics.

Michael J. Fox Foundation Young (PI) Design of HdAd Type 5 LRRK2 Expression Vectors 03/2013-12/2014

6/1/2016-3/2018

4/1/2015-3//31/2020

7/1/2014-8/31/2019

The goal of this project is to novel HdAd vectors with cell-specific tropism, production cell lines, genetic models, development of transgene cassettes for controlled expression, and surgical

8/1/2019-7/31/2021

7/2020-6/2023 Viral Vector Mediated Gene Therapy Approaches for Hearing and Balance Disorders The goal of this project is to work with MJFF to ensure that the HdAd Type 5 vectors produced are verified for particle to infectious genome/ml concentration

Michael J. Fox Foundation Young (PI)

Design of HdAd Type 5 LRRK2 Expression Vectors

The goal of this project is to design an HdAd LRRK2 expression vector that can be used by all Parkinson disease researchers. In particular, identify the sequence elements and design a transgene expression cassette to express LRRK2 that can be incorporated into a Helperdependent Adenoviral vector for in vivo studies.

1R21EY023408-01 NIH/NEI (PI: Young)

New Molecular Tools to Characterize Cortical Circuit Function in Non-Murine Mammals

The goal of this application is to begin to bridge a technology gap by developing a recombinant viral vector for use in non-murine mammals that will permit in vivo expression of molecular reporters and effectors using cell-type specific promoters. As proof of principle, we will generate and characterize a helper-dependent adenovirus (HdAd) vector that will allow the selective expression of genetically encoded fluorescent proteins and light-sensitive channels in GABAergic neurons of the ferret visual cortex. The availability of a viral construct that yields expression selectively in GABAergic neurons of non-murine mammals will make it possible to address a host of questions that are critical for understanding cortical function in health and disease.

Michael J. Fox Foundation (PI: Young)

Development of appropriate control transgenes for long term viral vector mediated gene transfer and optical imaging in the Substantia Nigra.

Using viral vectors to transfer PD disease genes directly to the substantia nigra as an animal model is gaining wide acceptance in the PD research community. Unfortunately, as the viral vectors have improved, the control genes, which are supposed to be neutral have been shown to show toxicity to dopamine neurons. This nigral pathology is problematic for the model. This project is designed to try to find a control gene that is safe for substantia nigra and can replace the currently used control gene.

PENDING Research Support:

HHMI Investigator competition

Molecular Principles of Auditory Information Processing

Our major research goal is to define the molecular principles underlying accurate sound information processing and explore how dysregulation contributes to hearing impairments that impact the quality of life.

D. INVITED LECTURES, CONFERENCE PRESENTATIONS, VISITING PROFESSORSHIPS

PANELS

Pills, Potions, Plagues, Pandemics—The Changing Role and Realm of Microbes. Princeton Alumni Faculty Forum Princeton University, Princeton, NJ. (2001) Princeton Alumni Faculty Forum Princeton University, Princeton, NJ. (2016) Healthcare: Taking the National Temperature Gordon Research Seminar "Synaptic Transmission" (Aug 11-17,2018) Navigating Careers in Science- Synaptic Transmission Gordon Research Seminar (2018) Gordon Research Conference Synaptic Transmission (2018) Power Hour-Women in Science University of Iowa- This is Us- Nov 11, 2022

3/21/2023

3/2013-3/2016

03/2012-03/2013

3/2013/-3/2015

SEMINARS NATIONAL 2003-prior

17th Annual Meeting of the American Society for Virology Vancouver, Canada (1998) Virology Seminar Series. University of North Carolina at Chapel Hill. (1998) MUSC Neuroscience series. Medical Unversity of South Carolina. (2002) UNC-CH Virology Colloquium.. University of North Carolina at Chapel Hill, (2000) Virology Seminar Series. University of North Carolina at Chapel Hill. (1999)

2004

34th annual Society for Neuroscience Meeting, San Diego, CA. Princeton Neuroscience Seminar Series.. Princeton University, Princeton, NJ

2008

Yale University Department of Physiology. New Haven, CT, USA (2008) Marine Biological Laboratories, Woodshole, MA USA (2008).

2010

Florida Atlantic University, Center of Molecular Biology and Biotechnology Novel University of Miami Miller School of Medicine, Dept of Physiology and Biophysics FAU/MPFI Neuroscience Symposium Florida Atlantic University, (Sept 28,29 2010)

2011

Minisymposium, "Exocytosis and vesicle trafficking" Max Planck Institute for Biophysical Chemistry Department of Membrane Biophysics. (Aug 18-19, 2011)

2012

University of Florida.Gene Therapy Center.

2013

Janelia Farms Research Campus, Ashburn, Virginia

2014

Ultrafast and temporally precise information processing: Normal and Dysfunctional Hearing Georgia Regents University, Augusta, GA Carnegie Mellon University, Pittsburgh, PA,

2015

Stanley Center, Broad Institute, Boston, MA Florida Atlantic University, Boca Raton, FL Scripps Florida, Jupiter, FL Georgia Regents, Augusta, GA TARAS meet the Scientist Lecture Series (April 8, 2015) Scripps Florida, Jupiter, Florida- Tri-Institutional Neuroscience Seminar Series University of Texas- Health Science Center San Antonio, San Antonio, TX

2016

Kresge Hearing Research Institute, University of Michigan, Ann Arbor, MI

University of Miami, Miami, FL Princeton University, Princeton, NJ University of South California, Los Angeles, CA University of Iowa, Iowa City, IA Minisymposium ARO MidWinter Meeting "Mechanisms of Fast Auditory Signaling" San Diego, CA (Feb20-24)

2017

Sunposium 2017- Jupiter Florida, USA Feb 13-14, 2017

2018

Vollum Institute, Portland, Oregon

2019

Aging Mind & Brain Symposium University of Iowa April 18, 2019 American Association of Anatomists Annual meeting Experimental Biology Orlando, Florida April 6-9 Caeser Institute, Bonn, Germany University of Iowa-Neuroscience Graduate student seminar series, Iowa City, IA

2020

University of Iowa Carver College of Medicine Weill Medical College, Cornell University MORE Seminar speaker Cal State University, (postponed) University of Colorado-School of Medicine (postponed) National Institute of Environmental Health and Safety (NIEHS)

2021

Columbia University University of Iowa SURF Program University of Iowa Molecular Medicine PhD program

2022

Vollum Institute University of California-Davis

2023

Tulane University University of Wisconsin-Madison University of Colorado-School of Medicine Illuminating the Druggable Genome Face-to Face Annual meeting Feb 28-Mar 1 Northeast Ohio Medical University

2024

Scripps Biomedical Research- University of Florida

INTERNATIONAL

2003- prior

8th annual Parvovirus Workshop. Mont-Tremblant, Quebec, Canada (2000)

2005

Center for the Investigation of Applied Medicine (CIMA) Department of Neurosciences, Pamplona, Spain.

University of Geneva. Dept of Biochemistry. Geneva, Switzerland

2007

Molecular Mechanisms of Exocytosis and Endocytosis, Jr. Investigator Meeting, University of Edinburgh. Edinburgh Scotland

MRC Toxicology, University of Leicester, England (2007) EPFL, Lausanne, Switzerland

2008

University of Toronto Department of Physiology. Toronto, Canada (2008) University of Leipzig, Institute of Biology II. Leipzig, Germany (2008).

2009

University of Seville, Laboratory of Neurotransmission (2009) Lemanic ENI network meeting Geneva, Switzerland (2009) Technical University of Munich Insitute of Neuroscience, Munich Germany (2009) Ludwig-Maximilians-University of Munich, Munich Germany Department of Neurobiology University of Innsbruck, Department of Pharmacology and Toxicology, Innsbruck, Austria. (2009)

2011

Minisymposium, "Exocytosis and vesicle trafficking" Max Planck Institute for Biophysical Chemistry Department of Membrane Biophysics. (Aug 18-19, 2011)

2012

Doshisha University, Kyoto, Japan

International Synapse Research workshop, "Understanding of synapse pathology, from genome mutation to functional defects" Okazaki Japan Nov 8-9, 2012

Gunma University, Dept of Neurophysiology, Maebashi Japan,

Gordon Research Conference. "Synaptic Transmission", (July 29-Aug 3,2012)

2014

Ultrafast and temporally precise information processing: Normal and Dysfunctional Hearing Methods Workshop "Targeted protein expression and conditional gene deletion in the auditory system" EPFL, Lausanne, Switzerland, (Nov 30 – Dec 3, 2014)

MiniSymposium "Membrane Biophysics" Max Planck Institute for Biophysical Chemistry Department of Membrane Biophysics. (Dec 5-6, 2014)

Gordon Research Conference, "Auditory Systems" July 8-13

Winter Conference on Brain Research, Steamboat Springs, Colorado (Jan 25- Jan 30, 2014)

2015

Erasmus University, Rotterdam, Netherlands Scripps Florida, Jupiter, FL FASEB Ion Channel Regulation Meeting 6/28-7/3/205) Max Planck Institute for Biophysical Chemistry University of Leipzig, Leipzig Germany

2016

University of Toronto & Sick Kids Research Institute, Toronto, Canada Institute of Science & Technology Austria, Vienna, Austria

2018

Gordon Research Conference. "Synaptic Transmission", (Aug 12-17,2018) The 12th international Symposium on Calcium Signaling in China (SCSC), Shenyang, P.R. China (July 18-22) Vollum Institute, Portland, Oregon Institute of Science and Technology Austria, Vienna, Austria International Brain Symposium, Tokyo Japan Feb 21-22 2018 University of Keio, Tokyo, Japan

2019

FASEB Ion Channel Regulation Conference: Molecules to Disease Lisbon Portugal July 7-12, Asklepios Biopharmaceutical Caeser Institute, Bonn, Germany Max Planck Institute for Biophysical Chemistry- MiniSymposium University of Goettingen, Goettingen, Germany

2020

Shenzen Synapse meeting, Shenzen China May 20-24 (postponed) National Institute of Environmental Health and Safety (NIEHS)

2022

European Calcium Channel Conference 2022 Alpach, Austria Raynor Cerebellar Project Sept 2022

2023

iGluR2023 Chicago, Illinois July 8-10 CACNA1A research Roundtable NY, NY Oct 9,10

2024

Neher Synapse Symposium, Goettingen, Germany March 14-16

IV. SERVICE

PROFESSONAL ACTIVITIES

Societies

Member, American Society for Virology, 1998-2000 Member, Society for Neuroscience, 2004-present Member, Association for Otolaryngology Research, 2013-present Member, Biophysical Society, 2017-present Member, American Association for Advancement of Science, 2019-present Member, Physiological Society, 2020-present Member, American Society of Gene&Cell Therapy 2021-present

Scientific Advisor

FBB Biomed, Inc7/2020-presentAsklepios BioPharmateuctical 7/2022-present

Reviewing Editor

Journal of Physiology 7/2020-present Physiological Reviews 1/2021-present

NIH Study section member

Auditory System Study Section (AUD) July 2021-present

Ad Hoc reviewing

Grant Reviewer, European Research Council	2010-12
Grant Reviewer, Swiss National Foundation	2010
Grant Reviewer, Michael J. Fox Foundation	2012
Grant Reviewer, NIH-AUD Study Section	Oct 8-9, 2015
Grant Reviewer, COBRE-NIH	Mar 14,2017
Grant Reviewer, ZRG1 MDCN-B(02) SEP	Oct 18,2017
Grant Reviewer, ZRG1 MDCN-M(02) SEP	Mar 14,2018
Grant Reviewer, Pfizer-NCBiotech Distinguished Postdoctoral	
Fellowships in Gene Therapy	2018,2019
Grant Reviewer, NIH- SYN Study section	Feb 13-14, 2020
Grant Reviewer, Wellcome Trust Investigator Awards	Oct 27,2020
Grant Reviewer, Austrian Science Fund (FWF)	Sept 19.2022

Journal Reviewer

Neuron, Journal of Neuroscience, Journal of Neurophysiology, Proceedings of the National Academy of Sciences, Cellular and Molecular Neurobiology, Molecular Therapy, Nature Neuroscience, Synapse, Frontiers in Neuroscience, Frontiers in Computational Biology, Journal of Physiology, PLOS Computational Biology, eLife, Biophysical Journal, Scientific Reports, Nature Communications, eNeuro, Developmental Neurobiology, Neuropharmacology, EMBO Journal, ACS Chemical Neuroscience, Molecular Psychiatry, Hearing Research, Neuropyschopharmacology, PLOS Biology, iScience, British Journal of Pharmacology, Guest Editor for Special Issue for the Synapse

Institutional Committees

Max Planck Florida

Max Planck Florida Institute for Neuroscience IACUC member 2010-2011

Max Planck Florida Institute for Neuroscience IBC member 2010-2012

Max Planck Florida Institute for Neuroscience IBC chair Oct 2012-Dec 2012

Max Planck Florida Institute for Neuroscience Light Microscopy Facility Committee 2014-2017

Max Planck Florida Institute for Neuroscience Electron Microscopy Core Committee 2014-2017

University of Iowa

Faculty advisor to University of Iowa Viral Vector Core 2017- present Iowa Neuroscience Institute Faculty Search Committee Member 2017- present Iowa Neuroscience Institute Seminar Committee 2019- present Department of Pediatrics Faculty Search Committee Chair, Winter 2022 University of Iowa Faculty Senate 7/2022-present Carver College Department review committee for Dept of Pediatrics Mar 7-8 2023

Conferences organized and chaired

Symposium Co-organizer- FAU/MPFI Neuroscience Symposium Sept 28-29 2010, Boca Raton, Florida

Calyx Symposium Co-organizer- Nov 12, 2011 NIH, Bethesda, Maryland Giant Synapse Symposium Co-Organizer Nov 14, 2014, NIH Bethesda, Maryland Co-Organizer Giant Synapse Symposium Oct 16, 2015, Chicago, Illinois Co-Organizer MiniSymposium "Mechanisms of Fast Auditory Signaling" ARO MidWinter

Meeting Feb 20-24, 2015. San Diego, California Co-Organizer Giant Synapse Symposium Nov 11, 2017, Washington, D.C. Organizer SFN Synapse Social Nov 14, 2017, Washington, D.C.

Chair/organizer American Association of Anatomists annual meeting at Experimental Biology 2019 "Synapses and Circuits: Form and Function April 6-9, 2019 Orlando, Florida

Co-Organizer Giant Synapse Symposium Oct 18, 2019 Chicago, Illinois Co-Organizer Iowa Neuroscience Institute Synapse Workshop, Sept 22-23, 2022 Co-Vice-Chair Gordon Research Conference Synaptic Transmission 2024 Co-Chair Gordon Research Conference Synaptic Transmission 2026