BIOGRAPHICAL SKETCH

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NAME: Juan Song

eRA COMMONS USER NAME (credential, e.g., agency login): JUAN_SONG

POSITION TITLE: Associate Professor (with tenure), Jeffery Houpt Distinguished Investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Nankai University (China)	B.S.	2001	Biology
University of California, Berkeley	Ph.D	2007	Neuroscience
Johns Hopkins University	Postdoctoral	2007-2013	Adult Neurogenesis

Personal Statement

The adult mammalian hippocampus contains endogenous neural stem cells (NSCs) that provide a self-renewable source for continuous replenishment of new neurons throughout life, thus highlighting the striking structural plasticity and regenerative capacity within the mature nervous system. In rodent models, adult-born neurons derived from neural stem cells in the dentate gyrus have been shown to play a causal role in specific forms of memory, such as spatial and contextual memory. Impaired memory, commonly associated with aging and Alzheimer's disease, correlates with impaired NSC behavior and hippocampal neurogenesis, thus suggesting that impaired hippocampal neurogenesis maybe a contributor to the cognitive decline associated with these conditions. The overarching goal of my research is to understand how the healthy adult brain regenerates from endogenous neural stem cells and apply basic learned principles to degenerated brains to promote regeneration and functional recovery. Over the past 7 years, we have been focusing our research to identify neuronal circuitry and signaling mechanisms that regulate distinct stages of adult hippocampal neurogenesis and investigate how circuit- and behavior-level information-processing properties are remodeled by the integration of new neurons into the existing circuits. We have established multifaceted approaches to investigate these directions, including circuit-based manipulation, retrograde/anterograde tracing, patch-clamp electrophysiology and calcium imaging of NSCs and various niche cells in acute slices, lineage tracing of adult neural precursor cells, and *in vivo* multi-fiber photometry recording during behavior.

Ongoing projects I would like to highlight include:

1. R01NS121300-01 Song (PI) 6/1/2021-5/31/2026
Role of cholecystokinin in the dentate gyrus

2. RF1AG071000-01 Song (PI) 3/1/2021-2/29/2024
Glutamatergic neural circuit modulation for treating Alzheimer's disease

3. R01MH122692-01 Song (PI) 2/1/2020 - 12/31/2024
Sex-dependent role of 5HT1A receptors in adult neurogenesis and hippocampal function

4. R01MH111773-01 Song (PI) 9/26/2016 - 8/31/2021 (NCE)
Neural circuitry mechanisms regulating adult hippocampal neurogenesis

Citations (*: corresponding author, #: equal contribution):

a. Song J, Zhong C, Bonaguidi MA, Sun G, Hsu D, Gu Y, Meletis K, Huang J, Ge S, Enikolopov G, Deisseroth K, Luscher B, Christian K, Ming GL, Song H (2012). Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision. ***Nature*** 489: 150-154

b. Bao H[#], Asrican B[#], Li W[#], Gu B, Wen ZX, Lim ZA, Haniff I, Ramakrishnan C, Deisseroth K, Philpot B, **Song J*** (2017). Long-range GABAergic inputs regulate neural stem cell quiescence and control adult hippocampal neurogenesis. **Cell Stem Cell** 21(5):604-617

c. Yeh CY[#], Asrican B[#], Moss J, Quintanilla L, He T, Mao X, Cassé F, Gebara E, Bao H, Lu W, Toni N, **Song J*** (2018). Mossy cells control adult neural stem cell quiescence and maintenance through a dynamic balance between direct and indirect pathways**. Neuron** 99(3):493-510

d. Li Y, Bao H, Luo Y, Yoan C, Sullivan HA, Quintanilla L, Wickersham IR, Lazarus M, Shin YY, **Song J*** (2020). Supramammillary nucleus synchronizes with dentate gyrus to regulate spatial memory retrieval through glutamate release. **eLife** doi: 10.7554/eLife.53129.

e. Asrican B[#], Wooten J[#], Li Y, Quintanilla L, Zhang F, Bao H, Yeh CY, Wander C, Luo YJ, Olsen RHJ, Lim SA, Jin P, **Song J*** (2020). Neuropeptides modulate local astrocytes to regulate adult hippocampal neural stem cells. **Neuron** 108(2):349-366

B. Positions, Scientific Appointments, and Honors

Positions

2019-present	Associate Professor, Department of Pharmacology, University of North Carolina, Chapel Hill
2018-present	Associate Director, Neuroscience Curriculum, University of North Carolina, Chapel Hill
2018-present	Faculty member, Intellectual and Developmental Disabilities Research Center, University of North Carolina, Chapel Hill
2013-present	Faculty member, Neuroscience Center, University of North Carolina, Chapel Hill
2013-2019	Assistant professor, Department of Pharmacology, University of North Carolina, Chapel Hill
2007- 2013	Postdoctoral fellow, Johns Hopkins University School of Medicine
2001- 2007	Graduate Student Researcher, University of California, Berkeley

Honors

Academic Award

2019	Jeffery Houpt Distinguished Investigator Award (UNC)
2018	Hettleman Award (UNC)
2018	Distinguished Lectureship (University of Toronto)
2016	American College of Neuropsychopharmacology (ACNP) Travel Award
2015	Junior Faculty Career Development Award (UNC)
2014	Janett Rosenberg Trubatch Career Development Award (Society for Neuroscience)
2014-2018	American Heart Association Scientist Development Award
2014-2017	Whitehall Foundation Award
2014-2016	NARSAD Young Investigator Award (Brain and Behavioral Research Foundation)
2013	Alfred Blalock Young Investigator Award (Johns Hopkins University)
2012	Julius Axelrod Postdoctoral Travel Award (Society for Neuroscience)
2011-2013	Maryland Stem Cell Research Foundation Postdoctoral Fellowship
2011	Keystone Symposia Scholarship (Adult Neurogenesis)
2008-2011	Life Sciences Research Foundation Postdoctoral Fellowship

Mentor Award

2019	Outstanding Postdoctoral Mentor Award (UNC)
2019	Mentor of the Year (UNC Neuroscience Curriculum)

Scientific Appointments

Editorial Board
Journal of Neuroscience, Frontiers in Neuroscience

Guest Editor
Neuroscience Letters (Special Issue)

Journal Reviewer
Neuron, Nature Neuroscience, Cell Stem Cell, Nature Medicine, Nature Communications, Science Advances, Journal of Clinical Investigation, Molecular Psychiatry, eLife, Cell Reports, PNAS, Journal of Neuroscience, Frontiers in Neuroscience, Frontiers in Molecular Neuroscience, Developmental Neurobiology, European Journal of Neuroscience; Journal of Neurochemistry, Journal of Neurophysiology, Molecular Brain

Grant reviewer
Member of NCF (Neurogenesis and Cell Fates) at NIH: 2021-2025

NIH ad hoc reviewer for NAL, NDPR, CDIN, MDCN-B, MDCN-G, MDCN-T, BDCN-F

Reviewer for Alzheimer's Association, American Heart Association, Swiss National Science Foundation, Dutch Research Council

Symposium Session Chair
Molecular Psychiatry Association (2019), Society for Neuroscience minisymposium (2019)

Membership
Society for Neuroscience

C. Contribution to Science
1. The early publications during my graduate school addressed how seizure is suppressed using *Drosophila* as a model system. Studies of human seizure disorders have revealed that susceptibility to seizures is largely influenced by genetic factors. In addition to causing epilepsy, genetic factors can also suppress seizures and epileptogenesis. Discovery of seizure-suppressor genes is challenging in mammals, however, such genes are readily identified and analyzed in a *Drosophila* model of epilepsy. Seizure-suppressor mutations in *Drosophila* are a novel class of second-site mutations that reverse the epilepsy phenotype of seizure-sensitive mutants. These mutations are a potentially powerful approach for identifying targets for anti-epileptic drugs. My accomplishments explored the potential of this approach, particularly: 1) Established an electrophysiology-based protocol for examining seizure-suppressor mutations utilizing a *Drosophila* mutation affecting the gap junction channel and reverse genetics. 2) Conducted a forward-genetics screen for new seizure-suppressor mutations, utilizing transposon mutagenesis, and discovered a novel mutation affecting DNA topoisomerase I. Mutations of topoisomerase I are especially effective at reverting the seizure phenotype of *Drosophila* epilepsy mutants. A creative model for seizure-suppression based on neuronal apoptosis is proposed and validated experimentally. 3) Based on the seizure suppression property of DNA topoisomerase I, I examined DNA topoisomerase I inhibitors as a promising new class of anti-epileptic drugs in *Drosophila* seizure models. DNA topoisomerase I inhibitors are a class of drug FDA-approved for cancer treatment, but not previously thought to be useful as anti-epileptic drugs.

a. **Song J*** and Tanouye M (2006). Seizure suppression by *shakB*^{2}, a gap junction mutation in *Drosophila*. ***J. Neurophysiology*** 95 (2): 627-635.

b. **Song J*,** Hu J and Tanouye M (2007). Seizure suppression by *top1* mutations in *Drosophila*.
J. Neuroscience 27 (11): 2927-2937.

c. **Song J*,** and Tanouye M (2007). Role for *para* sodium channel gene 3' UTR in the modification of *Drosophila* seizure susceptibility. ***Dev Neurobiol*** 67(14):1944-56.

d. **Song J*,** Parker L, Hormozi L and Tanouye M (2008). DNA topoisomerase I inhibitors ameliorate seizure-like behaviors and paralysis in a Drosophila model of epilepsy. ***Neuroscience*** 156(3):722-728.
(*: corresponding author)

2. Adult neurogenesis arises from neural stem cells within specialized niches. Neuronal activity and experience, presumably acting upon this local niche, regulate multiple stages of adult neurogenesis, from neural progenitor proliferation to new neuron maturation, synaptic integration and survival. Whether local neuronal circuitry has a direct impact on adult neural stem cells is unknown. To address this fundamental question, I have developed a novel system to study the interaction between niche components and adult neurogenesis. This system combines an optogenetic approach to selectively manipulate the activity of specific local interneuron subtypes and a genetic approach to sparsely label adult neural stem cells and their progeny for lineage-tracing and fate mapping. Using this system I identified, for the first time, dentate gyrus parvalbumin-expressing interneurons as a critical and unique niche component that conveys hippocampal circuit activity to the regulation of neural stem cell activation, proliferating neural progenitor survival, and immature neuron integration and excitatory synapse formation. Together, these studies uncovered fundamental circuit mechanisms by which local network activity regulates endogenous adult neurogenesis at distinct developmental stages.

a. **Song J,** Zhong C, Bonaguidi MA, Sun G, Hsu D, Gu Y, Meletis K, Huang J, Ge S, Enikolopov G, Deisseroth K, Luscher B, Christian K, Ming GL, Song H (2012). Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision. ***Nature*** 489: 150-154 *(Featured in Cell Stem Cell, Nat Rev Neurosci, BioEssays, F1000 must read)*

b. **Song J,** Sun J, Moss J, Wen Z, Sun G, Hsu D, Zhong C, Davoudi H, Christian K, Toni N, Ming GL, Song H (2013). Parvalbumin interneurons mediate neuronal circuitry-neurogenesis coupling in the adult hippocampus. ***Nature Neuroscience*** 16(12):1728-30

c. Kang E[#], **Song J[#] (co-first author)**, Lin Y, Park J, Lee JH, Hussani Q, Gu Y, Ge S, Li W, Berninger B, Hsu K, Christina K, Song H, Ming GL (2019). Interplay between a mental disorder risk gene and developmental polarity switch of GABA action leads to excitation-inhibition imbalance. **Cell Reports** 28(6):1419-1428

3. Adult neurogenesis recapitulates the whole process of neuronal development in a mature central nervous system, from proliferation and fate specification of adult neural progenitors, morphogenesis, migration, axon/dendritic development, and finally synapse formation, culminating in the full integration of new neurons into the existing circuitry. Cumulative evidence suggests that new neurons participate in specific brain functions and aberrant adult neurogenesis may contribute to brain disorders. During my postdoctoral studies, I use adult mouse hippocampal neurogenesis as an experimental model system to elucidate molecular mechanisms regulating the neuronal development. Furthermore, I use this system to explore novel functions of risk genes for mental disorders in neuronal development during the adult stage. Knowledge gained from these studies provide the basis for understanding the etiology of neurological diseases and mental disorders and have important implications for neuronal replacement therapy.

a. Kim JY, Liu CY, Zhang F, Duan X, Wen Z, **Song J**, Feighery E, Lu B, Rujescu D, St Clair D, Christian K, Callicott JH, Weinberger DR, Song H, Ming GL (2012). Interplay between DISC1 and GABA signaling regulates neurogenesis in mice and risk for schizophrenia. ***Cell*** 148(5):1051-64

b. Zhou M, Li W, Huang S, **Song J,** Kim JY, Tian X, Kang E, Liu C, Balaji J, Zhou Y, Parivash SN, Zhou Y, Ehninger D, He L, Song H, Ming GL, Silva AJ (2013) mTOR inhibition ameliorates cognitive and affective deficits caused by Disc1 knockdown specifically in adult-born dentate granule neurons. ***Neuron*** 77(4):647-54

c. Jang M, Kitabatake Y, Bonaguidi, MA, Sun J, **Song J,** Kang E, Jun H, Zhong C, Su Y, Guo J, Wang M, Sailor K, Kim JY, Gao Y, Christian KM, Ming GL, Song H (2013). Secreted frizzled-related protein 3 regulates activity-dependent adult hippocampal neurogenesis. ***Cell Stem Cell*** 12(2):215-23

d. Duan Y, Wang SH, **Song J**, Mironova Y, Song H, Kolodkin A, and Giger RJ (2014). Semaphorin 5A inhibits synaptogenesis in early postnatal- and adult-born hippocampal dentate granule cells. ***eLife*** Oct 14;3 ***(doi: 10.7554/eLife.04390)***

4. In my lab at UNC, Our primary research interests are: 1) To identify the circuit mechanisms that regulate neural circuit organization and function at distinct stages of adult neurogenesis, including activation and fate choice of quiescent neural stem cells, survival of proliferating neural progenitors, and synaptic integration of newborn neurons; 2) To understand how circuit-level information-processing properties are remodeled by the integration of new neurons into existing circuits and how dysregulation of this process may contribute to various neurological and mental disorders. Our long-range goals are to translate general principles governing neural network function into directions relevant for understanding neuropsychiatric diseases and neuronal replacement therapy for brain injuries. We are addressing these questions using a combination of innovative and multifaceted approaches, including *in vivo* multi-channel recording, patch-clamp electrophysiology, calcium imaging, optogenetics and chemogenetics, lineage tracing/fate mapping of adult neural stem/progenitor cells, retroviral-mediated approach for birthdating, high-resolution confocal microscopy, and sophisticated mouse genetic models.

a. Winkle C[#], Olsen RHJ[#], Kim H, Moy S, **Song J*,** Gupton S* (2016). TRIM9 deletion alters developing and adult born hippocampal neuron morphogenesis and impairs spatial learning and memory. ***J. Neuroscience*** 4;36(18):4940-58

b. Bao H[#], Asrican B[#], Li W[#], Gu B, Wen ZX, Lim ZA, Haniff I, Ramakrishnan C, Deisseroth K, Philpot B, **Song J*** (2017). Long-range GABAergic inputs regulate neurl stem cell quiescence and control adult hippocampal neurogenesis. **Cell Stem Cell** 21(5):604-617 **(Cover article, selected for preview, recommended by F1000, selected as one of the best articles in Cell Stem Cell in 2017)**

c. Yeh CY[#], Asrican B[#], Moss J, Quintanilla L, He T, Mao X, Cassé F, Gebara E, Bao H, Lu W, Toni N, **Song J*** (2018). Mossy cells control adult neural stem cell quiescence and maintenance through a dynamic balance between direct and indirect pathways**. Neuron** 99(3):493-510 **(selected for preview)**

d. Asrican B[#], Wooten J[#], Li Y, Quintanilla L, Zhang F, Bao H, Yeh CY, Wander C, Luo YJ, Olsen RHJ, Lim SA, Jin P, **Song J*** (2020). Neuropeptides modulate local astrocytes to regulate adult hippocampal neural stem cells. **Neuron** 108(2):349-366 **(selected for preview)**

(*: corresponding author; [#]: equal contribution)

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/juan.song.2/bibliography/public/