## BIOGRAPHICAL SKETCH

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NAME: Juan Song

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

POSITION TITLE: Professor (with tenure), Jeffrey 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 dentate gyrus (DG) within the hippocampal formation 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 (AD), 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 few years, we have made tremendous progress in dissecting 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 (**Song et al., *Nature* 2012; Song et al., *Nature Neuroscience* 2013; Bao et al., *Cell Stem Cell* 2017; Yeh et al., *Neuron* 2018; Asrican et al., *Neuron* 2020; Li et al., *Nature Neuroscience* 2022, Li et al., *Cell Stem Cell* 2023, Luo et al., *Cell Reports* 2024, Chen et al., *PNAS* 2024**). DG is not only a neurogenic region, but also the first input region to the hippocampus, which plays a critical role in regulating cognitive (i.e. learning and memory) and non-cognitive (i.e. anxiety- and depression- like behaviors) functions. Therefore, my lab is also interested in the neural circuit and signaling mechanisms regulating these broadly defined hippocampal functions using both healthy and AD mouse models (**Li et al., *eLife* 2020, Wander et al., Journal of Translational Medicine 2023, Xie et al., Nature Communications 2025**). We have established multifaceted approaches to investigate these directions, including circuit-based manipulation, retrograde/anterograde tracing, patch-clamp and in vivo electrophysiology, slice and in vivo calcium imaging, lineage tracing, single-cell RNA-sequencing, and proteomics to address these questions across cellular, molecular, circuit, and network levels.

### 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. R01AG071000-01 Song (PI) 3/1/2021-2/29/2026**
Glutamatergic neural circuit modulation for treating Alzheimer's disease

**3. R01MH122692-01 Song (PI) 2/1/2020 - 12/31/2025**
Sex-dependent role of 5HT1A receptors in adult neurogenesis and hippocampal function

**4. R01MH132222-A1 Song (PI) 7/6/2023 - 7/5/2028**
Regulation and functional contribution of hypothalamic modified adult hippocampal neurogenesis

**5. R01AG084207-01 Song (PI) 8/15/2023 - 8/14/28**
Enhancing adult-born neurons to restore brain functions in Alzheimer's disease

**Highlighted publications (*: corresponding author, #: equal contribution):**

**a.** 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 **(Cover article, Featured article with a preview, Best Articles in Cell Stem Cell 2017)**

**b.** 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 **(Featured article with a preview)**

**c.** Li YD#, Luo YJ#, Chen ZK, Quintanilla L, Cherasse Y, Zhang L, Lazarus M, Huang ZL, **Song J*** (2022). Hypothalamic modulation of adult hippocampal neurogenesis in mice confers activity-dependent regulation of memory and anxiety-like behavior. **Nature Neuroscience** 25(5):630-645 **(Featured in Nature Review Neuroscience)**

**d.** Li YD, Luo YJ, Xie L, Tart DS, Sheehy RN, Zhang L, Coleman Jr LG, Chen X, **Song J*** (2023). Activation of hypothamamic-enhanced adult-born neurons restores cognitive and affective functions in Alzheimer's disease. **Cell Stem Cell** 30(4): 415-432. **(Featured article with a preview)**

**B. Positions, Scientific Appointments, and Honors**

**Positions**

| | |
|---|---|
| 2023-present | 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 |
| 2019-2023 | Associate Professor, Department of Pharmacology, 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 | Jeffrey Houpt Distinguished Investigator (Endowed professorship, UNC) |
| 2018 | Philip and Ruth Hettleman Prize (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**

Nature, Science, Cell, Neuron, Nature Neuroscience, Cell Stem Cell, Nature Medicine, Nature Aging, Nature Communications, Science Translational Medicine, Science Advances, Advanced Science, Molecular Psychiatry, Journal of Clinical Investigation, Brain, Developmental Cell, PNAS, eLife, Cell Reports, Stem Cell Reports, Journal of Neuroscience, etc

**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 (2019), Spring Hippocampus Conference (2023, 2025)

**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.** AHN is dynamically regulated by neural activity, yet the precise circuit mechanisms governing this process remain poorly understood. Over the past 11 years, my lab has significantly advanced the field by uncovering multiple distinct neural circuits that regulate NSCs through both direct and indirect mechanisms. We discovered that forebrain GABAergic projections from the medial septum indirectly regulate NSCs through depolarizing GABA signaling onto dentate PV interneurons (***Bao et al., Cell Stem Cell 2017***), while forebrain cholinergic projections from the Diagonal Band of Broca modulate NSCs via dentate granule neurons (***Chen et al., PNAS 2024***). Additionally, we identified hilar mossy cells (MCs) as key regulators of NSCs, engaging in two distinct activity-dependent pathways: directly activating NSCs via glutamatergic inputs during high activity states and promoting NSC quiescence via PV interneurons during low activity states (***Yeh et al., Neuron 2018***). Beyond neuronal intermediaries, we uncovered a non-neuronal regulatory mechanism, where dentate cholecystokinin (CCK) interneurons signal through astrocytes to influence NSCs via gliotransmission (***Asrican et al., Neuron 2020***). Collectively, these discoveries redefine our understanding of NSC regulation by revealing two distinct modes of circuit-mediated control: (1) a direct mode, where local or distal circuits act directly on NSCs and modulate their function, and (2) an indirect mode, where neural circuits regulate intermediary niche cells that, in turn, modulate NSC function.

**a.** 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)**

**b.** 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 **(Featured article with a preview)**

**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 **(Featured article with a preview)**

**d.** Chen ZK, Quintanilla L, Su Y, Sheehy RN, Simon JM, Luo YJ, Li YD, Chen Z, Asrican B, Tart DS, Farmer WT, Ming GL, Song H, **Song J*** (2024) Septo-dentate gyrus cholinergic circuits modulate function and morphogenesis of adult neural stem cells through granule cell intermediaries. **Proceedings of the National Academy of Sciences** 2024 Oct;121(40):e2405117121

**4.** Despite significant progress in understanding circuit-based regulation of AHN, a fundamental question remains: Can neural circuit manipulation induce sufficient neurogenic effects to drive behavioral improvements? Recently, we identified the supramammillary nucleus (SuM), a key subcortical region in the hypothalamus, as a potent regulator of AHN. SuM sends dense projections to the DG, and its activation significantly enhances AHN (**Li et al., *Nature Neuroscience* 2022**). Specifically, patterned optogenetic stimulation of SuM neurons promotes NSC self-renewal, neurogenic proliferation, and ABN maturation, leading to an increased production of ABNs with enhanced developmental properties. Notably, chemogenetic modulation of SuM-enhanced ABNs bidirectionally regulates memory performance and anxiety-like behaviors. We further tested this strategy in Alzheimer's disease (AD) mouse models, where patterned SuM stimulation restored both the number and developmental properties of ABNs. Remarkably, acute activation of SuM-enhanced ABNs reversed memory deficits and alleviated anxiety- and depression-like behaviors in AD mice (**Li et al., *Cell Stem Cell* 2023**). These findings highlight the therapeutic potential of circuit-enhanced neurogenesis for cognitive enhancement in healthy brains and AD treatment.

**a.** Li YD[#], Luo YJ[#], Chen ZK, Quintanilla L, Cherasse Y, Zhang L, Lazarus M, Huang ZL, **Song J*** (2022). Hypothalamic modulation of adult hippocampal neurogenesis in mice confers activity-dependent regulation of memory and anxiety-like behavior. **Nature Neuroscience** 25(5):630-645 **(featured in Nature Review Neuroscience)**

**b.** Li YD, Luo YJ, Xie L, Tart DS, Sheehy RN, Zhang L, Coleman Jr LG, Chen X, **Song J*** (2023). Activation of hypothamamic-enhanced adult-born neurons restores cognitive and affective functions in Alzheimer's disease. **Cell Stem Cell** 30(4): 415-432. **(Featured article with a preview)**

**5.** DG is not only a neurogenic region, but also the first input region to the hippocampus, which plays a critical role in regulating cognitive (i.e. learning and memory) and non-cognitive (i.e. anxiety- and depression- like behaviors) functions. Therefore, my lab is also interested in the neural circuit and signaling mechanisms regulating these broadly defined hippocampal functions using both healthy and AD mouse models.

**a.** Wander C, Li YD, Bao H, Asrican B, Luo YJ, Sullivan H, Chen Z, Zhang L, Wickersham I, Shih YY, Cohen T, **Song J*** (2023). Compensatory remodeling of a septo-hippocampal GABAergic network in a triple transgenic Alzheimer's mouse model. **Journal of Translational Medicine** 15;21(1):258.

**b.** Xie L, Sheehy RN, Muneer A, Xiong Y, Wrobel JA, Zhang F, Park KS, Velez J, Liu J, Luo YJ, Asrican B, Dong P, Li YD, Damian C, Quintanilla L, Li Y, Xu C, Deshmukh M, Coleman LG Jr, Ming GL, Song H, Wen Z, Jin J*, **Song J*,** Chen X*. Development of a brain-penetrant G9a methylase inhibitor to target Alzheimer's disease-associated proteopathology. **Nature Communications** 16(1):4222. doi: 10.1038/s41467-025-59128-z.

**c.** 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.

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

**Complete List of Published Work in MyBibliography:**

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