OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

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NAME: Santhakumar, Vijayalakshmi

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

POSITION TITLE: Associate Professor, Molecular, Cell and Systems Biology, UC Riverside

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) | Completion Date  MM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Kilpauk Medical College, Chennai, India  University of California, Irvine, USA  University of California, Irvine, USA  University of California, Los Angeles, USA  UCLA School of Medicine, Los Angeles, USA | M.B.B.S (MD)  Ph.D.  Post-doc  Post-doc  Post-doc | 1989-1995  1998-01/2004  01/2004-06/2004  07/2004-04/2006  05/2006-10/2008 | Medicine and Surgery  Neuroscience  Neural Computation  Neurophysiology  Neurophysiology |

**A. Personal Statement:**

I have over 20-years’ experience studying the cellular and circuit mechanisms of epilepsy following unprovoked seizures and brain injury. A particular area of interest is physiological and circuit plasticity of diverse inhibitory neuronal populations including parvalbumin interneurons and their role in epilepsy, post-traumatic pathology and autism. My lab adopts a powerful combination of electrophysiological, molecular and immunohistological techniques with computational modeling to analyze the neural circuit structure and pathophysiology, with a focus on hippocampal inhibitory circuit plasticity. Using technically challenging recordings from interneuronal pairs, we have identified intrinsic synaptic and non-synaptic plasticity of dentate parvalbumin basket cells after seizures and adopted computational modeling to determine the functional consequences of these changes. Our studies in experimental models of epilepsy, supported by an active NIH R01 (5R01NS069861-11) which renewed in 2018, have revealed complex cell-type specific changes in inhibitory networks that affect network oscillations. My lab has led the field in analysis of inhibitory regulation of a novel class of excitatory neurons, semilunar granule cells, in the dentate circuit. Our optogenetic analysis has revealed cell specific contribution of parvalbumin interneurons to sustained feedback inhibition of semilunar granule cells which could shape their role in memory processing. Our studies have revealed unique inhibitory dysfunction in these novel class of dentate gyrus neurons after brain injury. Our studies perturbing molecular cues guiding parvalbumin neuron migration during development, have identified reduced synaptic inhibition of hippocampal pyramidal neurons which contribute to autistic behavioral phenotypes and heightened epileptogenicity. My lab also has had a long-standing interest in mechanisms of acquired epilepsy after traumatic brain injury. My lab analyzed multiple aspects of post-traumatic pathology including biomechanics of impact, circuit plasticity, metabolomics, neurogenesis and neuro-immune interactions. With support from an active NIH R01 (2R01NS097750-06, renewed in 2021) we are examining immune regulation of neurogenesis and neural plasticity and its impact on long-term cognitive dysfunction.

My lab provides a rich training experience in multidisciplinary and collaborative research into neurobiology of disease. I am passionate about mentoring a diverse student body to grow their individual strengths and develop essential career skills regardless of eventual career choice. Postdoctoral researchers and high school students alike have benefited from research experience in my lab and are now in research labs, industry, and STEM teaching. I actively support student’s efforts to implement new techniques and emphasize conceptual and critical literature review as well as training in technical approaches. Specific emphasis is placed on developing a sound understanding of experimental design, critical review of literature, research ethics and emphasis on rigor and reproducibility. I have a strong record of mentorship with three postdoctoral fellows, four PhDs and two MS trainees continuing in science/education. Three current students, including a first-generation graduate, have secured NRSA F31 predoctoral fellowships while a postdoctoral fellow was awarded a DoD Mentored Research Grant. A recent PhD graduate from my lab, a first-generation graduate, was awarded the 2018 Stanley S. Bergen Medal of Excellence by the Rutgers School of Graduate Studies. I have consistently encouraged student to attend and present at meetings (Society for Neuroscience, American Epilepsy Society, National Neurotrauma Society and Gordon research Conference) and participate in targeted training courses. I also have extensive collaboration on and off campus and trainees often interact with collaborating faculty on an individual basis. My commitment to multidisciplinary research, record of mentoring students and expertise in physiological and computational approaches will be an asset in successfully mentoring graduate students. Graduate students co-authoring selected publications are identified below.

Ongoing Research Support and **Trainee grants** I would like to highlight:

1. 2R01NS097750-06 NIH/NINDS (PI: Santhakumar) 9/01/2016-7/31/2026

Title: Contribution of innate immune receptors to neurological dysfunction after traumatic brain injury: Mechanisms and therapeutic implications

1. 5R01NS069861-11NIH/NINDS (PI: Santhakumar)  9/30/2011 – 7/31/2023

Title: Inhibitory Network Plasticity in Neurological Disease

1. **EP200042** DoD (PI: Subramanian; Role: Mentor) 07/2021-06/2024

Department of Defense, Idea Development - Research Partnership - 1

Title: Role of TLR4-Driven MMP-9 Activity in Functional Deficits and Epileptogenesis in Hippocampal Dentate Gyrus Following Traumatic Brain Injury

1. **F31NS124290** NIH/NINDS (PI: Dovek; Role: Mentor) 09/2021-08/2024

Title: Cellular and circuit mechanisms of hippocampal dentate engram formation and seizure-induced alterations

1. **F31NS120620** NIH/NINDS (PI: Nguyen; Role: Mentor) 07/2021-02/2024

Title: Role of TLR4 in Neuronal Excitability and Memory Function

1. **F31NS110220**  NIH/NINDS (PI: Corrubia; Role: Mentor) 09/2019-07/2022

Title: The Role of Adult-Born Neurons in Traumatic Brain Injury Induced Neuropathology

Citations:

1. Afrasiabi M, Gupta A, Xu H, Swietek B, **Santhakumar V** (2022). Differential Activity-Dependent Increase in Synaptic Inhibition and Parvalbumin Interneuron Recruitment in Dentate Granule Cells and Semilunar Granule Cells. *Journal of Neuroscience*. Jan 3: DOI: 10.1523/JNEUROSCI.1360-21.2021.
2. Eisenberg C, Subramanian D, Afrasiabi M, Ziobro P, DeLucia J, Hirschberg PR, Shiflett MW, **Santhakumar V**, Tran TS (2021). Reduced hippocampal inhibition and enhanced autism-epilepsy comorbidity in mice lacking neuropilin 2. *Translational Psychiatry*. 2021 Oct 18;11(1):537.
3. Korgaonkar AA, Li Y, Sekhar D, Subramanian D, Guevarra J, Palotti A, Singh S, Kella K, Swietek B, Elkabes S, **Santhakumar V** (2020), TLR4 signaling in neurons enhances calcium-permeable AMPAR currents and drives post-traumatic epileptogenesis. *Annals of Neurology*, Apr;87(4):497-515.
4. Yu J, Proddutur A, Swietek B, Elgammal F, **Santhakumar V** (2015) Functional reduction in Cannabinoid-Sensitive Heterotypic Inhibition of Dentate Basket Cells in Epilepsy: Impact on Network Rhythms. *Cerebral Cortex* Sep 22. pii: bhv199

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

**Positions and Employment**

07 2021- Vice Chair, Molecular Cell and Systems Biology, University of California at Riverside

02 2018- Associate Professor with Tenure, University of California at Riverside, Riverside

02 2018- Adjunct Associate Professor, Rutgers-New Jersey Medical School, Newark

07 2017-01 2018 Acting Associate Professor, Cedars Sinai Medical Center, Los Angeles

2016 Visiting Associate Professor, University of California, Irvine

2016-2018 Affiliated Associate Professor, New Jersey Institute of Technology, Newar

2014-2018 Associate Professor, Rutgers-New Jersey Medical School, Newark

Award of Tenure 2017

2013-2014 Assistant Professor, Rutgers-New Jersey Medical School, Newark

2008–2013 Assistant Professor, University of Medicine and Dentistry of New Jersey, Newark

2004-2008Postdoctoral Fellow, University of California, Los Angeles

2003-2004Postdoctoral Fellow, University of California, Irvine

1998-2003Graduate Student, University of California, Irvine

1997-1998Research Assistant, University of California, Irvine

1996-1997 Resident ENT Doctor, Govt. Madras Medical College Hospital, Chennai, India.

1995-1996 Hospitalist, Emergency Care, GG Hospital, Chennai, India.

1995-1996 Hospitalist, Emergency Care, Vasanthi Perinatology Research Foundation, Chennai, India.

**Other Scientific Appointments and Memberships**

2021 Chair, Scientific Program Committee of the AES

2020- Reviewing Editor, Journal of Neuroinflammation

2020- Reviewing Editor, eNeuro

2020- Associate Editor, Journal of Neuroscience

2020 - Member, American Association for the Advancement of Science

2018 -2021 Permanent member, NIH Peer Review Committee: Clinical Neuroplasticity and Neurotransmitters

2016-2018 Chair, Investigator Workshop Committee of the AES

2015 Vice Chair, Investigator Workshop Committee of the AES

2015 - 2020 Contributing Editor, Epilepsy Currents

2014-2016 Member, Scientific Program Committee of the AES

2014-2018 Member, Investigator Workshop Committee of the AES

2013 OASIS Leadership and Professional Development Program for Career Development and Advancement of Academic Women in STEM Fields, Rutgers, Newark, NJ

2011 -2017 NIH Peer Review Committee: Clinical Neuroplasticity and Neurotransmitters, ad hoc reviewer

2007 Summer Course on Imaging Structure and Function in Neuroscience and Development, Cold Spring Harbor Laboratory

2006 - Ad hoc Grant Reviewer, Citizens United for Research in Epilepsy (CURE) Foundation

2001 - Member, American Epilepsy Society

2000 - Member, Society for Neuroscience

Ad Hoc Reviewer: Biological Cybernetics, Brain, Brain, Behavior and Immunity, Brain Structure and Function, Cell reports, Cerebral Cortex, Chaos, European Journal of Neuroscience, eLife, eNeuro, Epilepsia, Experimental Neurology, Hippocampus, Journal of Neuroscience, Journal of Neurophysiology, Journal of Physiology, Nature Medicine, Nature Communications, Neurobiology of Disease, Neuropharmacology, NeuroReport, Neuroscience, Neuroscience Letters, PLOS-Computational Biology, Scientific Reports

**Honors**

2016 Moderator, Gordon Conference on Epilepsy and Neuronal Synchronization, Girona, Spain

2004 National Research Service Award for Postdoctoral Training- Institutional (2004-2006).

1998 UC-Regents Fellowship for Graduate Studies in Molecular Biology, Genetics and Biochemistry.

1994 First Certificate of Honor in Community Medicine, Kilpauk Medical College, Chennai, India.

1990 Gold Medal, Merit Certificate and Scholarship for outstanding performance in Biology, Department of Biotechnology-Ministry of Science and Technology, Government of India.

**C**. **Contribution to Science**

1. Interneuronal microcircuit plasticity in disease: My lab is using cutting edge paired interneuronal recordings, in vitro and in vivo optogenetics and large-scale computational modeling to identify inhibitory microcircuit plasticity in experimental epilepsy. We have identified a selective preservation of synaptic connection among fast-spiking basket cells and a reduction in heterosynaptic inputs form cannabinoid sensitive interneurons to basket cells. These data together with ongoing studies are aimed at identifying the inhibitory circuits that lead to altered network oscillation and could precipitate spontaneous seizures and memory and mood-related co-morbidities in epilepsy. Our recent studies examining Neuropilin 2, a critical repulsive molecular cue guiding cortical interneuron migration during development, have identified reduced parvalbumin neuron numbers in the hippocampus as well as a functional reduction in pyramidal cell inhibition. We find that developmental dysregulation of parvalbumin neuron circuit integration leads to reduced seizure threshold and behavioral phenotypes associated with autism consistent with the comorbid conditions of autism-epilepsy.

1. Eisenberg C, Subramanian D, Afrasiabi M, Ziobro P, DeLucia J, Hirschberg PR, Shiflett MW, **Santhakumar V**, Tran TS (2021). Reduced hippocampal inhibition and enhanced autism-epilepsy comorbidity in mice lacking neuropilin 2. *Translational Psychiatry*. 2021 Oct 18;11(1):537.
2. Yu J, Swietek B, Proddutur A, **Santhakumar V** (2016) Dentate cannabinoid-sensitive interneurons undergo unique and selective strengthening of mutual synaptic inhibition in experimental epilepsy. *Neurobiol. Dis.* 2016 May;89:23-35. DOI: 10.1016/j.nbd.2016.01.013.
3. Yu J, Proddutur A, Swietek B, Elgammal F, **Santhakumar V** (2015) Functional reduction in Cannabinoid-Sensitive Heterotypic Inhibition of Dentate Basket Cells in Epilepsy: Impact on Network Rhythms. *Cerebral Cortex* Sep 22. pii: bhv199 DOI: 10.1093/cercor/bhv199
4. Yu J\*, Proddutur A\*, Elgammal F, Ito T, **Santhakumar V** (2013). Depolarizing shift in GABA reversal limits network effects of enhanced basket cell tonic GABA currents after status epilepticus. *Journal of Neurophysiology.* 109(7):1746-63

2. Neuronal diversity and “non-canonical” excitatory and inhibitory neuronal players in dentate circuit: Although circuits abound with morphological and functional diverse neurons, studies in epilepsy and brain injury have largely focused on the major projection neurons and a few inhibitory neurons. My early collaborative studies revealed the profound impact that neuronal diversity has on network activity levels. My graduate and co-authored studies showed that dentate excitatory mossy cells could promote network excitability challenging the accepted paradigm that loss of these neurons enhances network excitability leading to epilepsy. Recently, studies from my lab using slice physiology and optogenetic tools have identified distinct inhibitory physiology of a novel dentate projection neuron, the semilunar granule cell, and show that their excitability is selectively enhanced after brain injury. In addition to driving studies examining cell-specific and activity dependent change in inhibition of semilunar granule cells, my lab has identified that dentate interneurons with axons spanning the molecular layer (TML neurons) are characterized by low reliability, low amplitude synapses modulated by cannabinoid receptors. In contrast to cannabinoid-expressing interneurons in the literature, TML cells do not label for cholecystokinin (CCK), indicating their distinctive neurochemical identity. Together these studies provide fundamental insights into the dentate microcircuit function and neuronal diversity and demonstrate the importance of looking beyond the canonical neuronal players to understand neuropathology and function.

1. Afrasiabi M, Gupta A, Xu H, Swietek B, **Santhakumar V** (2022). Differential Activity-Dependent Increase in Synaptic Inhibition and Parvalbumin Interneuron Recruitment in Dentate Granule Cells and Semilunar Granule Cells. *Journal of Neuroscience*. Jan 3: DOI: 10.1523/JNEUROSCI.1360-21.2021.
2. Gupta A, Proddutur A, Chang YJ, Raturi V, Guevarra J, Shah Y, Elgammal FS, **Santhakumar V.** (2020) Dendritic morphology and inhibitory regulation distinguish dentate semilunar granule cells from granule cells through distinct stages of postnatal development. *Brain Struct Funct*. Dec;225(9):2841-2855.
3. Yu J, Swietek B, Proddutur A, **Santhakumar V** (2015). Total Molecular Layer Interneurons: A Source of Cannabinoid-Sensitive Inhibition in the Dentate Gyrus. *Hippocampus.* DOI: 10.1002/hipo.22419.
4. **Santhakumar V**, Bender R, Frotscher M, Ross ST, Hollrigel GS, Toth Z, Soltesz I (2000). Granule cell hyperexcitability in the early post-traumatic rat dentate gyrus: the 'irritable mossy cell' hypothesis. *Journal of Physiology*. (London) 524 Pt 1: 117-134.

3. Identifying mechanistic underpinnings of post-traumatic seizure disorders: My early work provided the first conclusive evidence that a single concussive head injury results in a lasting decrease in threshold for seizure. My studies identified the long term structural and functional plasticity following brain injury, including the abnormal sprouting of recurrent excitatory collaterals in the dentate gyrus. These primary author studies spear headed research into post-traumatic epileptogenesis. In recent studies, my group has demonstrated distinctive early injury responses resulting from injuries with different physical characteristics, which has implications for clinical management blast-related injuries. My group has demonstrated that innate immune receptor toll-like receptor 4 (TLR4) contributes to early increase in dentate excitability after brain injury and that TLR4 signaling has diametrically opposite effects on network excitability in normal and injured brain. We further demonstrated that TLR4 effects after brain injury were driven by neuronally expressed TLR4 and that blocking TLR4 early after brain injury could limit subsequent development of epilepsy and memory deficits. However, we found a unique role for TLR4 in reducing basal circuit excitability in uninjured animals indicating role for TLR4 in regulation neurophysiology. These findings will help refine and limit adverse effects while targeting TLR4 signaling to limit neuropathology after brain insults, including trauma, stroke, and epilepsy. In related studies, we find that post-traumatic increase in neurogenesis is transient and gives way to depletion of the neurogenic pool which could adversely impact memory processing.

1. Korgaonkar AA, Li Y, Sekhar D, Subramanian D, Guevarra J, Palotti A, Singh S, Kella K, Swietek B, Elkabes S, **Santhakumar V** (2020), TLR4 signaling in neurons enhances calcium-permeable AMPAR currents and drives post-traumatic epileptogenesis. *Annals of Neurology*, Apr;87(4):497-515.
2. Korgaonkar AA, Li Y, Guevarra J, Pang KCH, **Santhakumar V** (2020). Distinct cellular mediators drive the Janus Faces of Toll-like Receptor 4 regulation of network excitability which impacts working memory performance after brain Injury. *Brain Behav Immun.* Apr 4:S0889-1591(19)31078-5.
3. Neuberger EJ, Swietek B, Corrubia L, Prasanna A, **Santhakumar V** (2017). Enhanced Dentate Neurogenesis after Brain Injury Undermines Long-Term Neurogenic Potential and Promotes Seizure Susceptibility. *Stem Cell Reports*, Sep 12;9(3):972-984. doi: 10.1016/j.stemcr.2017.07.015.
4. Li Y\*, Korgaonkar A\*, Swietek B , Wang J, Elgammal FS, Elkabes, S, **Santhakumar V**. (2015). Toll-like receptor 4 augments mossy cell AMPA currents and contributes to NMDA receptor-independent increase in dentate excitability after brain injury. *Neurobiology of Disease*. Feb;74:240-53 DOI: 10.1016/j.nbd.2014.11.021. \*Contributed equally

4. Circuit effects of extrasynaptic inhibition in neuronal modulation and disease: My earlier studies as well as ongoing studies in my lab have identified novel circuit effects of extrasynaptic GABAergic inhibition in several brain regions. My primary author studies in the cerebellum demonstrated the physiological contributions of alpha6 subunits to both phasic and tonic GABA currents and identified mechanisms by which neuroactive drugs including alcohol and anesthetics can impair cerebellar circuit function and motor coordination. I also demonstrated that tonic inhibition contributes to cell-type specific survival of striatal neurons during excitotoxicity. More recently, my group has demonstrated expression and changes in tonic GABA currents among specific hippocampal neurons in brain injury and epilepsy. Since interneuronal tonic inhibition can affect network oscillations, our results suggest a mechanism by which neuroactive compounds acting on extrasynaptic GABA receptors can impact memory formation.

1. Gupta A, Elgammal F, Proddutur A, Shah S, **Santhakumar V** (2012). Decreased Tonic Inhibition Contributes to Increase in Dentate Semilunar Granule Cell Excitability after Brain Injury. *Journal of Neuroscience.* 32(7): 2523-2537.
2. **Santhakumar V**, Meera P, Karakossian MK, Otis TS (2013). A reinforcing circuit action of extrasynaptic GABAA receptor modulators in the cerebellum. *PLoS ONE*. 8(8): e72976.
3. **Santhakumar V**, Jones RT, Mody I (2010). Developmental Regulation and Neuroprotective Effects of Striatal Tonic GABAa Currents. *Neuroscience.* 167(3):644-55.
4. **Santhakumar V**, Hanchar HJ, Wallner M, Olsen RW, Otis TS (2006). Contributions of the GABAA Receptor Subunit α6 to Phasic and Tonic Inhibition Revealed by a Naturally Occurring Polymorphism in the α6 Gene. *Journal of Neuroscience*. 26(12):3357-3364.

5. Development of dentate network simulations to study epileptogenesis: I developed biophysically realistic models of the major dentate cell types and implemented large-scale network simulations of the dentate gyrus to examine circuit plasticity in epilepsy. My early modeling studies established the importance of spatially restricted low levels of mossy fiber sprouting in the spread of dentate excitability. My computational model, considered a bench mark for the large-scale data-driven network modeling approach, is being implemented by several research groups to analyze dentate network function. In collaborative studies, I compiled a comprehensive connectivity matrix of the dentate developed a full-scale in-silico graph of the dentate gyrus, in combination with dynamic simulations, to provide the first quantitative graph theoretical analysis of a mammalian neuronal network. This model was and remains a powerful working circuit-level predecessor of the famed “blue brain” which remains under construction. Recent and ongoing work in my lab has expanded the model to enable analysis of the impact of interneuronal inhibition on dentate epileptogenesis and rhythms. These model systems have provided a valuable and readily-accessible tool for neurobiologists to analyze complex dentate network phenomena including epilepsy and memory processing.

1. Proddutur A, Yu J, Elgammal FS, **Santhakumar V** (2013). Seizure-induced plasticity of fast-spiking basket cell GABA currents modulates frequency and coherence of gamma oscillation in network simulations. *Chaos.* Dec;23(4):046109.
2. Dyhrfjeld-Johnsen J\*, **Santhakumar V**\*, Morgan R, Huerta R, Tsimring L, Soltesz I (2007). Topological Determinants of Epileptogenesis in Large-Scale Structural and Functional Models of the Dentate Gyrus Derived from Experimental Data. *Journal of Neurophysiology*. 97(2):1566-1587. \*Contributed equally
3. **Santhakumar V**, Aradi I, Soltesz I (2005). Role of Mossy Fiber Sprouting and Mossy Cell Loss in Hyperexcitability: A Network Model of the Dentate Gyrus Incorporating Cell Types and Axonal Topography. *Journal of Neurophysiology*. 93(1):437-53
4. Aradi I, **Santhakumar V**, Chen K, Soltesz I (2002) Postsynaptic effects of GABAergic synaptic diversity: regulation of neuronal excitability by changes in IPSC variance. *Neuropharmacology* 43: 511-522.

**Complete List of Published Work in MyBibliography**: <http://www.ncbi.nlm.nih.gov/sites/myncbi/vijayalakshmi.santhakumar.1/bibliography/46333138/public/?sort=date&direction=ascending>