# BIOGRAPHICAL SKETCH

NAME: CLINE, HOLLIS T

eRA COMMONS USER NAME (agency login): CLINEH

POSITION TITLE: Hahn Professor of Neuroscience

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE | Completion Date | FIELD OF STUDY |
|---|---|---|---|
| Bryn Mawr College | BA | 01/1977 | BIOLOGY, |
| University of California Berkeley | PHD | 01/1985 | Neurobiology Dept |
| Stanford University Medical Center, Stanford, CA | Postdoctoral Fellow | | Neurobiology 1989-1990 |
| Yale University, New Haven, CT | Postdoctoral Fellow | | Neurobiology 1985-1989 |

## A. Personal Statement

Dr. Hollis Cline is the Hahn Professor of Neuroscience in the Department of Molecular and Cellular Neuroscience at The Scripps Research Institute. She received her Ph.D. in Neurobiology from the University of California, Berkeley. Holly came to Scripps Research from Cold Spring Harbor Laboratory where she was a Professor of Neuroscience for 14 years and served as Director of Research. She has received many accolades during her career including the National Institutes of Health Director's Pioneer Award, which she received in 2005 to launch a large-scale project to understand the architecture, development, and plasticity of brain circuits. In 2012, Dr. Cline was named as a fellow of the American Association for the Advancement of Science. This is an honor bestowed upon members by their peers. Dr. Cline's work was recognized "for seminal studies of how sensory experience affects the development of brain structures and function and for generous national and international advisory service to neuroscience." She has served as a council member for the National Eye Institute and the National Institute of Neurological Disease and Stroke of the National Institutes of Health, and on the Blue Ribbon Panel for the National Institute of Child Health and Human Development. Dr. Cline was the President of the Society for Neuroscience in 2016.

The goal of the research in the Cline lab is to determine the mechanisms by which sensory experience affects the development of brain structures and function. The Cline lab has repeatedly been at the forefront of innovative technical advances, including in vivo time-lapse imaging, in vivo electroporation methods, viral gene transfer, serial section electron microscopy combined with in vivo time-lapse imaging, application of RNA interference to Xenopus and whole animal electrophysiological recordings of visual responses. Her studies have led to increased understanding of mechanisms controlling neurogenesis, synapse formation and plasticity, structural development of neurons and assembly of functional circuits. Her research has led to the discovery that neuronal activity regulates the development of the visual system through a variety of mechanisms, including changes in neuronal structure, synaptic strength, synaptogenesis and gene expression. Dr. Cline's studies have relevance to a variety of developmental neurological disorders such as Fragile X Syndrome, Rett Syndrome, autism spectrum disorders, and schizophrenia - which are the result of errors in the development of brain circuitry.

## B. Positions and Honors

### Positions and Employment

1985 - 1988 Postdoctoral Fellow, Yale University, Dept. of Biology, New Haven, CT
1989 - 1990 Postdoctoral Fellow, Stanford University, Dept of Molecular & Cellular Physiology, Stanford, CA
1990 - 1993 Assistant Professor, University of Iowa, Dept. of Physiology & Biophysics, Iowa City, IA
1994 - 1998 Associate Investigator, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
1998 - 2008 Charles and Marie Robertson Chair in Neuroscience, Cold Spring Harbor Laboratory, CSH, NY
2002 - 2006 Director of Research, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY

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| 2008 - | Professor, Molecular & Integrative Neurosciences Dept., The Scripps Research Institute, CA |
| 2008 - | Hahn Professor of Neuroscience, The Scripps Research Institute, La Jolla, CA |
| 2016 - | Director, Adjunct Professor, Dept. of Neurosciences, School of Medicine, UCSD, CA |
| 2016 - | Chair, Neuroscience Department, The Scripps Research Institute, La Jolla, CA |

## Other Experience and Professional Memberships

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|---|---|
| 1993 - 1996 | Study Section, National Science Foundation |
| 1997 - 2002 | Study Section, NIH - National Eye Institute |
| 1998 - 1998 | Reviewer, Spinal Cord Research Foundation |
| 2000 - 2005 | Executive Committee, Watson School of Biological Sciences |
| 2001 - 2004 | Program Committee, Society for Neuroscience |
| 2002 - 2006 | Council Member, Society for Neuroscience |
| 2004 - 2007 | Board of Scientific Counselors, NIH - National Institute of Neurological Disorders and Stroke |
| 2005 - 2006 | Co-Chair, Board of Scientific Counselors, NIH - National Institute of Neurological Disorders and Stroke |
| 2005 - 2006 | Co-Chair, Board of Scientific Counselors, NIH - National Institute of Neurological Disorders and Stroke |
| 2005 - 2010 | Director’s Pioneer Award, NIH |
| 2006 - 2006 | Review Panel, NIH - Director's Pioneer Award |
| 2006 - 2006 | Roadmap Meeting, National Institutes of Health |
| 2006 - 2013 | Associate, Neuroscience Research Program, Neurosciences Institute |
| 2008 - 2009 | Co-Director, Marine Biological Laboratory Course in Neurobiology |
| 2010 - 2013 | Secretary, Society for Neuroscience |
| 2010 - 2015 | Reviewer, March of Dimes |
| 2011 - 2011 | Next Decade Workshop of Molecular Neuroanatomy, NIH - NIDA |
| 2012 - 2013 | DIR Review Panel, NIH - National Institute of Child Health and Human Development |
| 2012 - 2015 | Council, NIH - National Eye Institute |
| 2014 - 2014 | IRP Review Committee, National Institute of Child Health and Human Development |
| 2014 - 2015 | Human Cell Types Advisory Council, Allen Institute for Brain Science |
| 2015 - 2016 | President, Society for Neuroscience |

## Honors

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|---|---|
| 1977 | High Honors in Undergraduate Research, Bryn Mawr College |
| 1979 | NIH Training Grant, UC Berkeley Neurobiology Group |
| 1985 | Fellowship, National Eye Institute |
| 1991 | Scholars Award in Neuroscience, McKnight |
| 1993 | Fellowship, Klingenstein |
| 1993 | Steps Summer Fellowship, The Marine Biological Laboratory |
| 1994 | Association Award, Cold Spring Harbor Laboratory |
| 1994 | Award in Medically-related Research, Patterson Trust |
| 1995 | Salary Award , National Down Syndrome Society |
| 1996 | Award, Eppley Foundation for Research |
| 1996 | Funding Award, Hoffritz |
| 1998 | Co-organizer, Banbury Meeting on CaMKII Structure and Function |
| 2003 | Scientific Reasoning and Logic Scholar, Leslie C. Quick Jr. Charitable Trust Foundation |
| 2003 | Session Chair, CSHL Meeting: Axon Guidance and Synaptic Plasticity |
| 2003 | Co-Organizer, EMBO meeting: Assembly of Neural Circuits |
| 2004 | Co-Organizer, Gordon Conference: Neural Development |
| 2004 | Session Chair, CSHL Meeting: Ion Channels, Receptors and Synapses |
| 2006 | Chair, Gordon Conference: Neural Development |

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| 2006 | Session Chair, CSHL Meeting: Axon Guidance |
| 2007 | Co-organizer, CSHL Meeting: Synapses: From Molecules to Circuits and Behavior |
| 2009 | Co-organizer, CSHL Meeting: Synapses: From Molecules to Circuits and Behavior |
| 2011 | Co-organizer, CSHL Meeting: Synapses: From Molecules to Circuits and Behavior |
| 2012 | Fellow, AAAS American Academy for the Advancement of Science |
| 2013 | Outstanding Mentor Award, The Scripps Research Institute |

## C. Contributions to Science

1. Mechanisms controlling the organization of sensory projections in the brain. Sensory projections in the brain are highly organized into spatial representations of the sensory world, such as topographic maps or ocular dominance columns. In the mid-1980's, evidence indicated that patterned activity is required for the development of organized projections, but the mechanisms underlying activity-dependent control of topographic map formation were not known. As a postdoctoral fellow with Martha Constantine-Paton, I demonstrated that NMDA receptors are required for development and maintenance of retinotopic maps and ocular dominance columns in the frog retinotectal projection (Cline et al 1987). Later in my lab at Cold Spring Harbor Laboratory, we demonstrated that postsynaptic NMDA receptors located on tectal neurons regulate axon arbor dynamics within the target (Ruthazer et al, 2003). Together, this work demonstrated the role of NMDA receptors in activity-dependent map formation. Studies in many other experimental systems and other sensory projections corroborated our findings (Constantine-Paton et al, 1990). This body of literature is largely interpreted as demonstrating that Hebbian coactivity rules govern map formation, and was famously summarized as 'Neurons the fire together, wire together'. Although the Hebbian coactivity rules have provided a valuable framework in which to interpret the role of activity in organizing brain connections, we recently conducted a surprisingly simple experiment that provided evidence for a new activity rule governing map formation based on the temporal sequence of activity in the retina. This work is summarized as 'Neurons that fire in sequence, wire in sequence'. The data indicate that a temporal code of activity in the retinal instructs the spatial organization of retinal axons within the brain (Hiramoto & Cline, 2014). It is likely that this rule describing a spatial to temporal to spatial transformation of information in the visual system will be widely applicable to organized projections throughout the brain.

    a. Cline HT, Debski EA, Constantine-Paton M. N-methyl-D-aspartate receptor antagonist desegregates eye-specific stripes. Proc Natl Acad Sci U S A. 1987 Jun;84(12):4342-5. PubMed PMID: 2884663; PubMed Central PMCID: PMC305081.

    b. Constantine-Paton M, Cline HT, Debski E. Patterned activity, synaptic convergence, and the NMDA receptor in developing visual pathways. Annu Rev Neurosci. 1990;13:129-54. PubMed PMID: 2183671.

    c. Ruthazer ES, Akerman CJ, Cline HT. Control of axon branch dynamics by correlated activity in vivo. Science. 2003 Jul 4;301(5629):66-70. PubMed PMID: 12843386.

    d. Hiramoto M, Cline HT. Optic flow instructs retinotopic map formation through a spatial to temporal to spatial transformation of visual information. Proc Natl Acad Sci U S A. 2014 Nov 25;111(47):E5105-13. PubMed PMID: 25385606; PubMed Central PMCID: PMC4250144.

2. Activity-dependent Mechanisms of Synapse Maturation, Dendritic & Axonal Arbor Development. We have devoted considerable effort to understand the complex interplay by which activity-dependent mechanisms regulate neuronal development and plasticity in the context of an intact functional circuit. We developed methods for time-lapse in vivo imaging using laser scanning confocal microscopy combined with single cell labeling with fluorescent markers and used these state of the art methods to document the structural dynamics that occur during dendritic and axon arbor development in intact animals. We further showed that dendritic arbor dynamics are regulated by synaptic activity and that visual stimulation directly regulates neuronal structural activity (Sin et al 2002). We built our first two photo microscope in ~2001 by modifying an Olympus microscope using Karel Svoboda's plans. This instrument was essential for rapid time-lapse imaging studies that demonstrated minute-to-minute structural dynamics in axon and dendritic branches in intact animals. We were the first lab to use 2 photon time-lapse imaging of complete axonal and dendritic arbors to identify cellular and molecular mechanisms underlying structural plasticity (Sin et al, 2002;

Ruthazer et al 2003). We developed viral gene transfer methods and electroporation methods to regulate gene expression in neurons in vivo, which allowed us to manipulate activity-dependent signaling molecules, such as CaMKII, and show that glutamatergic synaptic activity and downstream CaMKII activity regulate the elaboration of neuronal dendrites by controlling the dynamic rates of branch additions and retractions. By incorporating electrophysiological assays of synapse formation and maturation with data on structural plasticity, we demonstrated the integral interaction between synaptic plasticity and structural plasticity (Wu et al 1996, Wu & Cline, 1998). We knew that rapid activity-dependent structural plasticity in dendritic arbors, however a direct relation between structural plasticity shown at the light microscope and ultrastructural rearrangements in synaptic connectivity was unclear. We conducted a tour-de-force series of experiments in which we collected time-lapse in vivo 2 photon imaging data demonstrating structural plasticity of dendrites over hours and days, and then generated complete serial section transmission electron microscope reconstructions of the same neurons. These datasets demonstrated the startling degree of synaptic rearrangements that occur in dynamic dendritic branches and highlighted the magnitude of synaptic loss and synaptic consolidation that occur during microcircuit refinement. These foundational studies are now the heart of the modern framework for activity-dependent control of neuronal development and circuit plasticity.

a. O'Rourke NA, Cline HT, Fraser SE. Rapid remodeling of retinal arbors in the tectum with and without blockade of synaptic transmission. Neuron. 1994 Apr;12(4):921-34. PubMed PMID: 8161460.
b. Wu G, Malinow R, Cline HT. Maturation of a central glutamatergic synapse. Science. 1996 Nov 8;274(5289):972-6. PubMed PMID: 8875937.
c. Wu GY, Cline HT. Stabilization of dendritic arbor structure in vivo by CaMKII. Science. 1998 Jan 9;279(5348):222-6. PubMed PMID: 9422694.
d. Sin WC, Haas K, Ruthazer ES, Cline HT. Dendrite growth increased by visual activity requires NMDA receptor and Rho GTPases. Nature. 2002 Oct 3;419(6906):475-80. PubMed PMID: 12368855.
e. Ruthazer ES, Akerman CJ, Cline HT. Control of axon branch dynamics by correlated activity in vivo. Science. 2003 Jul 4;301(5629):66-70. PubMed PMID: 12843386.
f. Li J, Erisir A, Cline H. In vivo time-lapse imaging and serial section electron microscopy reveal developmental synaptic rearrangements. Neuron. 2011 Jan 27;69(2):273-86. PubMed PMID: 21262466; PubMed Central PMCID: PMC3052740.

3. Function of activity regulated genes in brain circuit development. Hundreds of genes are induced by activity in the brain. Furthermore the synthesis, function and degradation of many proteins are regulated by neuronal activity. We have demonstrated the function of several activity-induced genes and activity-regulated proteins in neuronal and circuit development, starting with our early studies on the role of aCaMKII in dendritic arbor development, glutamate receptor trafficking and synaptic maturation, mentioned above. We also collaborated with Paul Worley and Elly Nedivi, both of whom had conducted early screens to identify activity-induced neural genes, to analyze the cellular and molecular functions of activity-regulated genes/proteins in neuronal development, plasticity and circuit assembly in a highly assessable vertebrate system. We produced a series of papers, including those listed below, which demonstrate that activity-regulated mechanisms impinge on circuit development by regulating such diverse cellular events as AMPAR trafficking, axon pathfinding, dendritic arbor development, cytoskeletal dynamics and protein synthesis. This work has contributed to basic understanding of the iterative role of activity and activity-induced gene and protein transcription/translation in circuit development.

a. Nedivi E, Wu GY, Cline HT. Promotion of dendritic growth by CPG15, an activity-induced signaling molecule. Science. 1998 Sep 18;281(5384):1863-6. PubMed PMID: 9743502; PubMed Central PMCID: PMC3088013.
b. Rial Verde EM, Lee-Osbourne J, Worley PF, Malinow R, Cline HT. Increased expression of the immediate-early gene arc/arg3.1 reduces AMPA receptor-mediated synaptic transmission. Neuron. 2006 Nov 9;52(3):461-74. PubMed PMID: 17088212; PubMed Central PMCID: PMC3951199.
c. Chiu SL, Chen CM, Cline HT. Insulin receptor signaling regulates synapse number, dendritic plasticity, and circuit function in vivo. Neuron. 2008 Jun 12;58(5):708-19. PubMed PMID: 18549783; PubMed Central PMCID: PMC3057650.

d. Bestman JE, Cline HT. The RNA binding protein CPEB regulates dendrite morphogenesis and neuronal circuit assembly in vivo. Proc Natl Acad Sci U S A. 2008 Dec 23;105(51):20494-9. PubMed PMID: 19074264; PubMed Central PMCID: PMC2629308.

4. Visual experience-dependent Regulation of Circuit Development and Plasticity. Sensory input activates both excitatory and inhibitory synaptic inputs and coordinated excitatory and inhibitory activity is required for synaptic plasticity and circuit stability. We have devoted considerable effort to understand the complex interplay by which activity-dependent mechanisms regulate inhibitory and excitatory function in the context of an intact sensorimotor circuit, using molecular genetic manipulations, in vivo time-lapse structural and functional imaging, electrophysiology, and behavioral analyses to assess multiple outcome measures. We provided foundational evidence that molecular genetic inhibition of GABAergic transmission interferes with normal development of tectal neuron dendritic arbors, increases the excitation/inhibition ratio in tectal neurons, and interferes with both visual information processing and sensorimotor function, assessed behaviorally in the intact animal (Shen et al, 2011). In a complimentary set of experiments, we used molecular genetic tools to interfere with glutamatergic synaptic maturation and demonstrated that excitatory synaptic dysfunction leads to cell-autonomous decreases in inhibitory synaptic function, which then ramifies to impair neuronal and circuit properties and degrade behavioral performance. These data provide direct evidence for an essential role for glutamatergic excitatory transmission in the cell autonomous development of GABAergic inhibition, which may be relevant to a variety of neurological diseases including autism spectrum disorder (He et al, 2018). Xenopus offers the opportunity to examine events at stages of brain circuit development that are inaccessible in other experimental systems. At early stages of tectal development, excitatory and inhibitory neurons can't be distinguished by morphological or electrophysiological features. Surprisingly, we found that two types of inhibitory neurons can be distinguished based on their opposite plasticity responses to brief visual experience. We hypothesize that the two types of inhibitory neurons function in circuit motifs that permit both synapse-specific plasticity and homeostatic circuit stability (He et al 2016). In addition, both excitatory and inhibitory neurons extend axons across an intertectal commissure. We demonstrated using imaging, electrophysiology and molecular genetic manipulations of excitatory and inhibitory receptor trafficking, that intertectal projections maintain the ratio of excitation to inhibition within a functional range required for visual avoidance behavior (Gambrill et al 2016, 2018).

   a. Shen W, McKeown CR, Demas JA, Cline HT. Inhibition to excitation ratio regulates visual system responses and behavior in vivo. J Neurophysiol. 2011 Nov;106(5):2285-302. PubMed PMID: 21795628; PubMed Central PMCID: PMC3214097.

   b. He, HY, Shen, W. Zheng, L., Guo, X., Cline, H.T. (2018) Cell-autonomous regulation of structural and functional plasticity in inhibitory neurons by excitatory synaptic inputs. Nature Communications (in press).

   c. He HY, Shen W, Hiramoto M, Cline HT. Experience-Dependent Bimodal Plasticity of Inhibitory Neurons in Early Development. Neuron. 2016 Jun 15;90(6):1203-14. PubMed PMID: 27238867; PubMed Central PMCID: PMC4938159.

   d. Gambrill AC, Faulkner R, Cline HT. Experience-dependent plasticity of excitatory and inhibitory intertectal inputs in Xenopus tadpoles. J Neurophysiol. 2016 Aug 31;PubMed PMID: 27582296; PubMed Central PMCID: PMC5110636.

   e. Gambrill, A.C., Faulkner, R.L., and Cline, H.T. (2018). Direct intertectal inputs are an integral component of the bilateral sensorimotor circuit for behavior in Xenopus tadpoles. J. Neurophysiol Faulkner R, Cline HT. PMID:29442555.

5. Exosome-mediated intercellular signaling in brain circuit development. Brain circuit development takes advantage of diverse mechanisms for intercellular signaling. We wrote a perspective about exosomes, in which we postulated that extracellular vesicles, including exosomes, may signal during brain development (Sharma et al 2013) and pursued this question in an hIPSC model of Rett Syndrome, an inherited type of autism spectrum disease. To examine exosome-mediated signaling events, we established productive collaborations with Dr. John Yates, an outstanding colleague here at the Scripps Research Institute who is a world-renown expert in mass spectrometric methods, and with Dr. Alysson Muotri, at UCSD, an expert in use of hIPSC to investigate human neurodevelopmental diseases. First, we improved methods to detect and quantify biotin-labeled proteins (Schiapparelli et al, 2014). With this expertise in hand, we conducted a

quantitative comparative proteomic analysis of exosome cargo released from hiPSC-derived neural cultures from Rett patient cell line or CRISPR corrected controls. The analysis demonstrated a significant enrichment in neurogenic proteins in control exosomes compared to a paucity of neurogenic proteins in exosomes from Rett neural cells. We validated the proteomic data with extensive imaging-based assays of exosome bioactivity in human cells (Sharma et al 2017).

a. Sharma P, Schiapparelli L, Cline HT. Exosomes function in cell-cell communication during brain circuit development. Curr Opin Neurobiol. 2013 Dec;23(6):997-1004. PubMed PMID: 23998929; PubMed Central PMCID: PMC3830597.
b. Schiapparelli LM, McClatchy DB, Liu HH, Sharma P, Yates JR 3rd, Cline HT. Direct detection of biotinylated proteins by mass spectrometry. J Proteome Res. 2014 Sep 5;13(9):3966-78. PubMed PMID: 25117199; PubMed Central PMCID: PMC4156236.
c. Sharma, P., Mesci, P., Carromeu, C., McClatchy, D., Schiapparelli, L., Yates, J., Muotri, A., and Cline, H.T. (2017). Exosomes regulate Neurogenesis and Circuit Assembly in a Model of Rett Syndrome. BioRxiv 168955.

6. Novel Mechanisms controlling Neurogenesis and Neural Circuit Development. Mechanisms regulating neurogenesis and neuronal differentiation are not completely understood. To address this gap, we conducted a number of studies investigating neurogenesis in the visual system of Xenopus tadpoles, where neural progenitors can be isolated for transcriptomic analysis, labeled for in vivo lineage tracing analysis and manipulated by expressing antisense oligonucleotides or genes of interest. We previously demonstrated that neurogenesis is regulated by visual activity, such that the neural progenitor pool expands when animals are dark-reared and then newly generated cells differentiate into neurons in response to visual stimulation, essentially operating 'on demand' to build the visual system (Sharma & Cline, 2010). Subsequently, we established in vivo imaging strategies to examine the lineage and differentiation of neural progenitors (Bestman et al, 2012) and then conducted an in vivo imaging- and RNAi-based screen to identify novel activity-regulated candidates regulating neurogenesis (Bestman et al 2015). Initial candidates were identified by differential expression of transcripts in neural progenitor cells in response to sensory experience. This screen identified 24 candidate neurogenic regulatory genes that have diverse cellular functions, suggesting that further analysis will identify more candidates. Importantly, the screen identified neurogenic defects resulting from knockdown of fmr1a, which encodes the Fragile X Mental Retardation Protein (FMRP), the protein that is lost in Fragile X Syndrome, as well as fxr1, a related transcript, and several transcripts whose translation is thought to be regulated by FMRP. We have conducted a more detailed study, which indicates that FMRP regulates neurogenesis in vivo by controlling neural progenitor cell proliferation and survival, as well as initial events in neuronal differentiation (Faulkner et al 2015). These exciting data suggest that loss of FMRP, as occurs in Fragile X Syndrome, may affect early events in brain development, and that studying FMRP function in neurogenesis may reveal novel functions of FMRP as well as novel mechanisms by which neurogenesis is regulated.
   a. Sharma P, Cline HT. Visual activity regulates neural progenitor cells in developing xenopus CNS through musashi1. Neuron. 2010 Nov 4;68(3):442-55. PubMed PMID: 21040846; PubMed Central PMCID: PMC3005332.
   b. Bestman JE, Lee-Osbourne J, Cline HT. In vivo time-lapse imaging of cell proliferation and differentiation in the optic tectum of Xenopus laevis tadpoles. J Comp Neurol. 2012 Feb 1;520(2):401-33. PubMed PMID: 22113462; PubMed Central PMCID: PMC3366109.
   c. Bestman JE, Huang LC, Lee-Osbourne J, Cheung P, Cline HT. An in vivo screen to identify candidate neurogenic genes in the developing Xenopus visual system. Dev Biol. 2015 Dec 15;408(2):269-91. PubMed PMID: 25818835; PubMed Central PMCID: PMC4584193.
   d. Faulkner RL, Wishard TJ, Thompson CK, Liu HH, Cline HT. FMRP regulates neurogenesis in vivo in Xenopus laevis tadpoles. eNeuro. 2015 Jan-Feb;2(1):e0055. PubMed PMID: 25844398; PubMed Central PMCID: PMC4384423.

7. Dynamics of Protein Synthesis in the Brain. The brain processes information, makes decisions, mediates cognitive and motor outputs through the functions of proteins in different types of connected neurons organized in complex arrangements. Although experience-dependent transcriptional dynamics have been extensively studied, comparable knowledge about the proteome is woefully incomplete. Current estimates indicate that there are 21,000 genes and 250,000 - 1 million different proteins in humans. We showed that the RNA binding protein, CPEB, is required for developmental and experience-dependent dendritic arbor

development and for visual information processing in vivo (Bestman et al, 2008). An important next step in understanding brain plasticity and function is to generate an accurate knowledgebase of protein changes in the intact brain in response to activity and sensory input. In collaboration with Dr. John Yates, an outstanding colleague at the Scripps Research Institute who is a world-renown expert in mass spectrometric methods, we have developed methods to query changes in protein constituents and distribution that can be applied to intact animals, using BONCAT, bio-orthogonal noncanonical amino acid detection, which uses incorporation of the noncanonical amino acid, azidohomoalanine (AHA), following by click chemistry tagging with biotin, to label newly synthesized proteins. To identify experience-dependent changes brain proteomics that might contribution to brain development and plasticity, we conducted proteomic studies in Xenopus visual system by labeling newly synthesized proteins with the non-canonical amino acid, AHA. Surprisingly, we found that synthesis of CPEB itself is increased by visual experience and that the newly-synthsized CPEB is required for experience-dependent behavioral plasticity (Shen et al 2014). Inspired by these unexpected findings, we conducted an unbiased screen to identify proteins whose synthesis is regulated by visual experience. This data provided the first brain proteomic data from Xenopus and importantly, identified novel candidate plasticity proteins whose function in experience-dependent plasticity had not been previously recognized (Liu et al 2018).

a. Bestman JE, Cline HT. The RNA binding protein CPEB regulates dendrite morphogenesis and neuronal circuit assembly in vivo. Proc Natl Acad Sci U S A. 2008 Dec 23;105(51):20494-9. PubMed PMID: 19074264; PubMed Central PMCID: PMC2629308.
b. Shen W, Liu HH, Schiapparelli L, McClatchy D, He HY, Yates JR 3rd, Cline HT. Acute synthesis of CPEB is required for plasticity of visual avoidance behavior in Xenopus. Cell Rep. 2014 Feb 27;6(4):737-47. PubMed PMID: 24529705; PubMed Central PMCID: PMC3962200.
c. Liu HH, McClatchy DB, Schiapparelli L, Shen W, Yates III JR, Cline HT. (2018). Role of the visual experience-dependent nascent proteome in neuronal plasticity. eLife, *7*, e33420. Elife. 2018 Feb 7;7. pii: e33420. doi: 10.7554/eLife.33420. PubMed PMID: 29412139; PubMed Central PMCID: PMC5815848.

**Complete List of Published Work in My Bibliography:** http://1.usa.gov/1IrUz68

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**Papers**

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Cline, H.T. (1983) 3H-GABA uptake selectively labels identifiable neurons in the leech central nervous system. J. Comp. Neurol. 215:351-358. PMID: 6853778

Cline, H.T. Nusbaum, M.P. and Kristan, W., Jr. (1985) Identified GABA-ergic inhibitory motor neurons in the leech central nervous system take up GABA. Brain Res. 348:359-362. PMID: 4075094

Cline, H.T. (1986) Evidence for GABA as a neurotransmitter in the leech. J. Neurosci. 6:2848-2856. PMID: 2876064

Glover, J.C., Stuart, D.K., Cline, H.T., McCaman, R.E., Magill, C., and Stent, G.S. (1987) Development of neurotransmitter metabolism in embryos of the leech *Haementeria ghilianii*. J. Neurosci. 7:581-594. PMID: 2880941

Cline, H.T., Debski, E. and Constantine-Paton, M. (1987) NMDA receptor antagonist desegregates eye-specific stripes. Proc. Natl. Acad. Sci. 84:4342-4345. PMCID:PMC305081

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Cline, H.T. and Constantine-Paton, M. (1989) NMDA receptor antagonist disrupts the retinotectal topographical map. Neuron 3:413-426. PMID:2577128

Cline, H.T. and Constantine-Paton, M. (1990) NMDA receptor agonist and antagonists alter retinal ganglion cell arbor structure in the developing frog retinotectal projection. J. Neurosci. 10:1197-1216. PMID:2158526

Debski, E.A., Cline, H.T. and Constantine-Paton, M. (1990) Activity-dependent tuning and the NMDA receptor. J. Neurobiol. 21:18-32. PMID: 2156953

Constantine-Paton, M., Cline, H.T. and Debski, E. (1990) Patterned activity, synaptic convergence and the NMDA receptor in developing visual pathways. Ann. Rev. Neurosci. 13:129-54. PMID: 2183671

Cline, H.T. and Constantine-Paton, M. (1990) The differential influence of protein kinase inhibitors on retinal arbor morphology and eye-specific stripes in the frog retinotecal system. Neuron 4:889-908. PMID: 2361013

Cline, H.T. (1991) Activity-dependent plasticity in the visual systems of frogs & fish. Trends in Neurosciences. 14:104-111. PMID: 1709534

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Cline, H.T., McDonald, J. W. and Constantine-Paton, M. (1994) Glutamate receptor binding in juvenile and adult Rana pipiens CNS. J. Neurobiol. 25: 488-502. PMID: 8071657

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Wu, G-Y, Zou, D-J, Koothan, T., and Cline, H.T. (1995) Infection of frog neurons with Vaccinia Virus permits in vivo expression of foreign proteins. Neuron 14: 681-684. PMID: 7718230

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