Stanford



Lu Chen

Professor of Neurosurgery and of Psychiatry and Behavioral Sciences

CONTACT INFORMATION

- **Administrative contact**

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Bio

ACADEMIC APPOINTMENTS

- Professor, Neurosurgery
- Professor, Psychiatry and Behavioral Sciences - Interdisciplinary Brain Sciences
- Member, Bio-X
- Member, Maternal & Child Health Research Institute (MCHRI)
- Member, Wu Tsai Neurosciences Institute

ADMINISTRATIVE APPOINTMENTS

- Professor, Department of Psychiatry and Behavioral Science, (2016- present)
- Associate Professor, Department of Psychiatry and Behavioral Science, (2011- present)
- Professor, Department of Neurosurgery, (2016- present)
- Associate Professor, Stanford Institute of Neuro-Innovation and Translational Neuroscience, (2011- present)

HONORS AND AWARDS

- NRSA Postdoc fellowship, NIH (2001)
- Beckman Young Investigator Award, Beckman foundation (2003)
- NARSAD Young Investigator Award, NARSAD (2005)
- Packard Fellow in Science and Engineering, David and Lucile Packard Foundation (2005)
- Keck Distinguished Young Scholar in Medical Research, W. M. Keck Foundation (2005)
- MacArthur Fellowship, MacArthur Foundation (2005)

BOARDS, ADVISORY COMMITTEES, PROFESSIONAL ORGANIZATIONS

- External Advisory Board member, Neuroscience and Brain Disease Research Center, China Medical University, Taiwan (2022 - present)
- Society for Neuroscience Young Investigator Award Selection Committee, Society for Neuroscience (2022 - present)
- Editorial Board, Current Opinion in Neurobiology (2019 - present)

- Senior Editor, eLife (2019 - present)
- Editorial Board, PLOS One (2018 - present)
- Editorial Board, Frontiers in Synaptic Neuroscience (2018 - present)
- Program Committee, Society for Neuroscience (2009 - 2012)
- Associate Editor, The Journal of Neuroscience (2008 - 2013)
- member, Society for Neuroscience (1993 - present)

PROFESSIONAL EDUCATION

- PhD, University of Southern California , Neurobiology (1998)

LINKS

- Chen Lab website: http://neurosurgery.stanford.edu/research/chen/index.html

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

The long-term goal of my research is to understand the cellular and molecular mechanisms that underlie synapse function during behavior in the developing and mature brain, and how synapse function is altered during mental retardation. In this broad research area, I am specifically interested in the homeostatic control of synaptic strength, the role of postsynaptic protein translation in this control, and the impairment of synapses in Fragile X syndrome that involves changes in postsynaptic protein translation and synaptic strength.

We recently discovered a role of all-trans retinoic acid (RA) in regulating synapse formation and synaptic strength, which we identified during studies of homeostatic synaptic plasticity. We found that RA is a potent activator of synaptic strength in mature neurons. Neuronal synthesis of RA is regulated by activity. When neuronal activity is blocked, RA synthesis is strongly stimulated. When applied directly, RA is sufficient to rapidly increase synaptic strength. Moreover, when we blocked RA synthesis in neurons, we abolished the increase in synaptic strength induced by activity blockade. Taken together, these results reveal a central role of RA in mediating activity blockade-induced increases in synaptic strength, and suggest that in adult brain, RA functions as a novel diffusible messenger that regulates synaptic transmission.

Subsequent experiments revealed that the synaptic effect of RA operates by stimulating the synthesis and insertion of new postsynaptic AMPA-receptors into existing synapses. What mediates the translational regulation function of RA? Combining electrophysiological, biochemical and ultrastructural approaches, we identified a novel role of the RA-receptor RARα in translational regulation. We found that RAR directly associates with specific RNA sequences in the 5'UTR of target mRNAs, and represses their translation. RA, by binding to RAR, releases this translational repression, probably by inducing a conformational change in RAR that leads to its dissociation from mRNA. To our knowledge, this is the first characterized translational regulatory mechanism that operates in a ligand-gated fashion.

How does the RA-dependent translational regulation intersect with other known mechanisms involved in dendritic protein synthesis and synaptic plasticity? We have recently found that the Fragile X Mental Retardation Protein (FMRP), an RNA-binding protein that regulates local protein translation in dendrites, is essential for increases in synaptic strength induced by RA or by neural activity blockade. Activity-dependent RA synthesis is maintained in Fmr1 knockout neurons, but RA-dependent activation of dendritic translation of AMPA-type glutamate receptors is impaired. Furthermore, we showed that the deficit in synaptic scaling in Fmr1 knockout neurons can be rescued by acute postsynaptic expression of FMRP, indicating that the role of FMRP is not developmental, but that it is part of the homeostatic synaptic machinery. Taken together, these findings identify an unexpected role for FMRP in regulating homeostatic synaptic plasticity downstream of RA. Our results raise the possibility that at least some of the symptoms of Fragile X syndrome,

a form of mental retardation caused by loss of FMRP function, reflect impaired homeostatic plasticity and dysfunctional RA signaling, and suggest that modification of the RA-signaling pathway in homeostatic plasticity may be beneficial for treating this prevalent disorder.

Teaching

STANFORD ADVISEES

Doctoral Dissertation Reader (AC)

Leyi Huang, Rennie Kendrick, Cheyanne Lewis, Shreya Malhotra, Riley Merkel

Doctoral Dissertation Advisor (AC)

Theo Ruffins

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Neurosciences (PhD Program)
- Psychiatry and Behavioral Science (Fellowship Program)

Publications

PUBLICATIONS

- **Editorial: Synaptic plasticity and dysfunction, friend or foe?** *Frontiers in synaptic neuroscience*
  Nugent, F. S., Li, K. W., Chen, L.
  2023; 15: 1204605
- **Retinoic acid-gated BDNF synthesis in neuronal dendrites drives presynaptic homeostatic plasticity.** *eLife*
  Thapliyal, S., Arendt, K. L., Lau, A. G., Chen, L.
  2022; 11
- **Spinal cord retinoic acid receptor signaling gates mechanical hypersensitivity in neuropathic pain.** *Neuron*
  Cao, B., Scherrer, G., Chen, L.
  2022
- **The ins and outs of neurexins in homeostatic plasticity and learning**
  Chen, L., Tjia, M., Arendt, K. L.
  WILEY.2022: 23-24
- **Homeostatic plasticity and excitation-inhibition balance: The good, the bad, and the ugly.** *Current opinion in neurobiology*
  Chen, L., Li, X., Tjia, M., Thapliyal, S.
  2022; 75: 102553
- **Identification of cis-regulatory modules for adeno-associated virus-based cell type-specific targeting in the retina and brain.** *The Journal of biological chemistry*
  Lin, C. H., Sun, Y., Chan, C. S., Wu, M. R., Gu, L., Davis, A. E., Gu, B., Zhang, W., Tanasa, B., Zhong, L. R., Emerson, M. M., Chen, L., Ding, et al
  2022: 101674
- **FMRP Interacts with RAR alpha in Synaptic Retinoic Acid Signaling and Homeostatic Synaptic Plasticity** *INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES*
  Park, E., Lau, A. G., Arendt, K. L., Chen, L.
  2021; 22 (12)
- **An analog of psychedelics restores functional neural circuits disrupted by unpredictable stress.** *Molecular psychiatry*
  Lu, J., Tjia, M., Mullen, B., Cao, B., Lukasiewicz, K., Shah-Morales, S., Weiser, S., Cameron, L. P., Olson, D. E., Chen, L., Zuo, Y.
  2021
- **Cell-type-specific profiling of human cellular models of fragile X syndrome reveal PI3K-dependent defects in translation and neurogenesis.** *Cell reports*

Raj, N., McEachin, Z. T., Harousseau, W., Zhou, Y., Zhang, F., Merritt-Garza, M. E., Taliaferro, J. M., Kalinowska, M., Marro, S. G., Hales, C. M., Berry-Kravis, E., Wolf-Ochoa, M. W., Martinez-Cerdeno, et al
2021; 35 (2): 108991

- **Defective memory engram reactivation underlies impaired fear memory recall in Fragile X syndrome.** *eLife*
  Li, J. n., Jiang, R. Y., Arendt, K. L., Hsu, Y. T., Zhai, S. R., Chen, L. n.
  2020; 9
- **The Quest for the Hippocampal Memory Engram: From Theories to Experimental Evidence.** *Frontiers in behavioral neuroscience*
  Miry, O., Li, J., Chen, L.
  2020; 14: 632019
- **Synaptic retinoic acid receptor signaling mediates mTOR-dependent metaplasticity that controls hippocampal learning** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Hsu, Y., Li, J., Wu, D., Sudhof, T. C., Chen, L.
  2019; 116 (14): 7113–22
- **Synaptic retinoic acid receptor signaling mediates mTOR-dependent metaplasticity that controls hippocampal learning.** *Proceedings of the National Academy of Sciences of the United States of America*
  Hsu, Y., Li, J., Wu, D., Sudhof, T. C., Chen, L.
  2019
- **Kinase pathway inhibition restores PSD95 induction in neurons lacking fragile X mental retardation protein.** *Proceedings of the National Academy of Sciences of the United States of America*
  Yang, Y. n., Geng, Y. n., Jiang, D. n., Ning, L. n., Kim, H. J., Jeon, N. L., Lau, A. n., Chen, L. n., Lin, M. Z.
  2019
- **Retinoic acid receptor RARalpha-dependent synaptic signaling mediates homeostatic synaptic plasticity at the inhibitory synapses of mouse visual cortex.** *The Journal of neuroscience : the official journal of the Society for Neuroscience*
  Zhong, L., Chen, X., Park, E., Sudhof, T. C., Chen, L.
  2018
- **Homeostatic synaptic plasticity as a metaplasticity mechanism-a molecular and cellular perspective.** *Current opinion in neurobiology*
  Li, J., Park, E., Zhong, L. R., Chen, L.
  2018; 54: 44–53
- **The fragile X mutation impairs homeostatic plasticity in human neurons by blocking synaptic retinoic acid signaling.** *Science translational medicine*
  Zhang, Z., Marro, S. G., Zhang, Y., Arendt, K. L., Patzke, C., Zhou, B., Fair, T., Yang, N., Sudhof, T. C., Wernig, M., Chen, L.
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- **Postnatal ablation of synaptic retinoic acid signaling impairs cortical information processing and sensory discrimination in mice.** *The Journal of neuroscience : the official journal of the Society for Neuroscience*
  Park, E., Tjia, M., Zuo, Y., Chen, L.
  2018
- **Postsynaptic synaptotagmins mediate AMPA receptor exocytosis during LTP** *NATURE*
  Wu, D., Bacaj, T., Morishita, W., Goswami, D., Arendt, K. L., Xu, W., Chen, L., Malenka, R. C., Sudhof, T. C.
  2017; 544 (7650): 316-?
- **The Retromer Supports AMPA Receptor Trafficking During LTP** *NEURON*
  Temkin, P., Morishita, W., Goswami, D., Arendt, K., Chen, L., Malenka, R.
  2017; 94 (1): 74-?
- **A metaplasticity view of the interaction between homeostatic and Hebbian plasticity** *PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B-BIOLOGICAL SCIENCES*
  Yee, A. X., Hsu, Y., Chen, L.
  2017; 372 (1715)
- **Integrating Hebbian and homeostatic plasticity: the current state of the field and future research directions** *PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B-BIOLOGICAL SCIENCES*

Keck, T., Toyoizumi, T., Chen, L., Doiron, B., Feldman, D. E., Fox, K., Gerstner, W., Haydon, P. G., Huebener, M., Lee, H., Lisman, J. E., Rose, T., Sengpiel, et al
2017; 372 (1715)

- **Differential regulation of spontaneous and evoked inhibitory synaptic transmission in somatosensory cortex by retinoic acid.** *Synapse*
X Yee, A., Chen, L.
2016; 70 (11): 445-452

- **Calcineurin mediates homeostatic synaptic plasticity by regulating retinoic acid synthesis.** *Proceedings of the National Academy of Sciences of the United States of America*
Arendt, K. L., Zhang, Z., Ganesan, S., Hintze, M., Shin, M. M., Tang, Y., Cho, A., Graef, I. A., Chen, L.
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- **Aldehyde dehydrogenase 1a1 mediates a GABA synthesis pathway in midbrain dopaminergic neurons.** *Science*
Kim, J., Ganesan, S., Luo, S. X., Wu, Y., Park, E., Huang, E. J., Chen, L., Ding, J. B.
2015; 350 (6256): 102-106

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Anderson, G. R., Aoto, J., Tabuchi, K., Foeldy, C., Covy, J., Yee, A. X., Wu, D., Lee, S., Chen, L., Malenka, R. C., Suedhof, T. C.
2015; 162 (3): 593-606

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2015; 86 (2): 442-456

- **Synaptic retinoic acid signaling and homeostatic synaptic plasticity.** *Neuropharmacology*
Chen, L., Lau, A. G., Sarti, F.
2014; 78: 3-12

- **Accelerated Experience-Dependent Pruning of Cortical Synapses in Ephrin-A2 Knockout Mice** *NEURON*
Yu, X., Wang, G., Gilmore, A., Yee, A. X., Li, X., Xu, T., Smith, S. J., Chen, L., Zuo, Y.
2013; 80 (1): 64-71

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Sarti, F., Zhang, Z., Schroeder, J., Chen, L.
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- **Rapid single-step induction of functional neurons from human pluripotent stem cells.** *Neuron*
Zhang, Y., Pak, C., Han, Y., Ahlenius, H., Zhang, Z., Chanda, S., Marro, S., Patzke, C., Acuna, C., Covy, J., Xu, W., Yang, N., Danko, et al
2013; 78 (5): 785-798

- **AMPA receptor/TARP stoichiometry visualized by single-molecule subunit counting.** *Proceedings of the National Academy of Sciences of the United States of America*
Hastie, P., Ulbrich, M. H., Wang, H., Arant, R. J., Lau, A. G., Zhang, Z., Isacoff, E. Y., Chen, L.
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- **Conditional RAR alpha knockout mice reveal acute requirement for retinoic acid and RAR alpha in homeostatic plasticity** *FRONTIERS IN MOLECULAR NEUROSCIENCE*
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2012; 5

- **Decrease in Calcium Concentration Triggers Neuronal Retinoic Acid Synthesis during Homeostatic Synaptic Plasticity** *JOURNAL OF NEUROSCIENCE*
  Wang, H., Zhang, Z., Hintze, M., Chen, L.
  2011; 31 (49): 17764-17771
- **Acute knockdown of AMPA receptors reveals a trans-synaptic signal for presynaptic maturation** *EMBO JOURNAL*
  Tracy, T. E., Yan, J. J., Chen, L.
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- **Fragile X Protein FMRP Is Required for Homeostatic Plasticity and Regulation of Synaptic Strength by Retinoic Acid** *JOURNAL OF NEUROSCIENCE*
  Soden, M. E., Chen, L.
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- **Retinoic acid-gated sequence-specific translational control by RAR alpha** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Poon, M. M., Chen, L.
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- **Synaptic Signaling by All-Trans Retinoic Acid in Homeostatic Synaptic Plasticity** *NEURON*
  Aoto, J., Nam, C. I., Poon, M. M., Ting, P., Chen, L.
  2008; 60 (2): 308-320
- **Retinoic acid regulates RAR alpha-mediated control of translation in dendritic RNA granules during homeostatic synaptic plasticity** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Maghsoodi, B., Poon, M. M., Nam, C. I., Aoto, J., Ting, P., Chen, L.
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  Aoto, J., Chen, L.
  2007; 1184: 72-80
- **Postsynaptic EphrinB3 promotes shaft glutamatergic synapse formation** *JOURNAL OF NEUROSCIENCE*
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- **Dynamics of postsynaptic glutamate receptor targeting** *CURRENT OPINION IN NEUROBIOLOGY*
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- **Postsynaptic assembly induced by neurexin-neuroligin interaction and neurotransmitter** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
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- **Functional studies and distribution define a family of transmembrane AMPA receptor regulatory proteins** *JOURNAL OF CELL BIOLOGY*
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  2003; 161 (4): 805-816
- **Direct interactions between PSD-95 and stargazin control synaptic AMPA receptor number** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Schnell, E., Sizemore, M., Karimzadegan, S., Chen, L., Bredt, D. S., Nicoll, R. A.
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- **Cerebellar cortical inhibition and classical eyeblink conditioning** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
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- **Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms** *NATURE*
  Chen, L., Chetkovich, D. M., Petralia, R. S., Sweeney, N. T., Kawasaki, Y., Wenthold, R. J., Bredt, D. S., Nicoll, R. A.
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- **Learning- and cerebellum-dependent neuronal activity in the lateral pontine nucleus** *BEHAVIORAL NEUROSCIENCE*
  Bao, S. W., Chen, L., Thompson, R. F.
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- **Impaired cerebellar synapse maturation in waggler, a mutant mouse with a disrupted neuronal calcium channel gamma subunit** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Chen, L., Bao, S. W., Qiao, X. X., Thompson, R. F.
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- **Transgenic brain-derived neurotrophic factor modulates a developing cerebellar inhibitory synapse** *LEARNING & MEMORY*
  Bao, S. W., Chen, L., Qiao, X. X., Thompson, R. F.
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- **Bilateral lesions of the interpositus nucleus completely prevent eyeblink conditioning in Purkinje cell-degeneration mutant mice** *BEHAVIORAL NEUROSCIENCE*
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- **Impaired eye-blink conditioning in waggler, a mutant mouse with cerebellar BDNF deficiency** *LEARNING & MEMORY*
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- **Cerebellar brain-derived neurotrophic factor-TrkB defect associated with impairment of eyeblink conditioning in stargazer mutant mice** *JOURNAL OF NEUROSCIENCE*
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  Bao, S. W., Chen, L., Thompson, R. F.
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- **Selective enhancement of emotional, but not motor, learning in monoamine oxidase A-deficient mice** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
  Kim, J. J., Shih, J. C., Chen, K., Chen, L., Bao, S. W., Maren, S., Anagnostaras, S. G., Fanselow, M. S., DEMAEYER, E., Seif, I., Thompson, R. F.
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  Thompson, R. F., Bao, S. W., Chen, L., Cipriano, B. D., Grethe, J. S., Kim, J. J., Thompson, J. K., Tracy, J. A., Weninger, M. S., Krupa, D. J.
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- **Deficient cerebellar long-term depression, impaired eyeblink conditioning, and normal motor coordination in GFAP mutant mice** *NEURON*
  Shibuki, K., Gomi, H., Chen, L., Bao, S. W., Kim, J. S., Wakatsuki, H., Fujisaki, T., Fujimoto, J., Katoh, A., Ikeda, T., Chen, C., Thompson, R. F., Itohara, et al
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- **Impaired motor coordination correlates with persistent multiple climbing fiber innervation in PKC gamma mutant mice** *CELL*
  Chen, C., Kano, M., Abeliovich, A., Chen, L., Bao, S. W., Kim, J. J., HASHIMOTO, K., Thompson, R. F., Tonegawa, S.
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