

# Curriculum Vitae

## Christopher D. Link

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## Education

B.S., Biology	1976	Brooklyn College, Brooklyn, NY
Ph.D. Microbiology	1981	University of Massachusetts, Amherst, MA

## Research and professional experience

9/76 - 6/77 Teaching Asst., Dept. of Microbiology, University of Massachusetts

9/77 - 12/81 NIH Graduate Trainee, Dept. of Microbiology, U. of Massachusetts

1/82 - 7/88 NIH Postdoctoral Research Fellow, Research Associate, Dept. of Molecular, Cellular and Developmental Biology, University of Colorado, Boulder

8/88 - 6/95 Assistant Professor, University of Denver

9/95 - 3/05 Senior Research Associate, University of Colorado

3/05 – 8/12 Associate Research Professor, University of Colorado

9/12 - Associate Professor, Integrative Physiology, University of Colorado

## Current Funding:

### **"Sleep Disruption and Alzheimer's Disease Pathology"**

This proposal seeks to determine the cellular mechanisms underlying the bidirectional interactions between sleep and Alzheimer's disease

R01 AG064465(Opp)	7/01/2019-6/30/2024
NIH	C. D. Link, MPI

NIH/NIA

C. D. Link, MPI

### **"Functions of Tau protein in human neural cells"**

In this study, we will use hiPSC-derived neural cells to examine how loss of tau function affects key neurodegenerative phenotypes including neuroimmune pathways, cellular stress and DNA damage, and neuronal electrophysiological function.

R21 AG079161 (Young)  
NIH

4/2023 – 3/2025  
C. D. Link, Co-I

**Previous Research Funding:**

**"C. elegans as a Model of Cell Senescence and Alzheimer's Disease"**

This proposal seeks to determine if senolytic drugs will modify phenotypes of transgenic C. elegans engineered to model aspects of Alzheimer's disease.

1 R21 AG067147-01 (Johnson)

4/01/2020 - 3/30/23

**"TDP-43, RNA Metabolism, and ALS/FTD Pathology"**

The goal of this project is to extend our observation that TDP-43 limits the accumulation of double stranded RNA to cellular models and pathological material.

R01 NS063964-06  
HHS/NINDS

8/1/15-7/30/20  
C. D. Link, PI

**"Enduring reversal of chronic pain by adenosine 2a agonism"**

The goal of this proposal is to investigate the novel hypothesis that an adenosine 2a receptor (A2aR) agonist can induce long-lasting relief from pain mediated by the anti-inflammatory actions of IL-10.

R21 NS102932-01A1  
L. Watkins, PI

7/1/18 - 6/30/20  
C. D. Link, Co-PI

University of Colorado Innovative Seed Grant "A $\beta$  as an immune modulator"  
**\$49,855** 7/30/2015-7/30/17

Linda Crnic Institute Grand Challenge Grant Award "Transcriptome analysis in paired trisomic/disomic Down syndrome cells"  
**\$ 199,832** 4/1/13-3/30/15

NIH R01 NS063964-01 "Investigation of TDP-43 Function and Toxicity in C. elegans"  
**\$1,800,000** 4/1/09-3/31/15

R01 AG012423-12 "Transgenic C. elegans as amyloid disease model"  
**\$1,715,160** 4/15/08-3/30/013

Alzheimer's Association Zenith Award "Structure/function analysis of *in vivo* beta amyloid peptide toxicity"  
**\$250,000** 9/1/07-8/31/09

NIH R01 AG021037 "Comparative Modeling of Neurodegenerative Diseases"  
**\$1,173,180** 6/01/03-5/30/08

Alzheimer's Association Temple Award TLL-01-2752 " Investigation of Proteins that Directly Interact with Intracellular Abeta Peptide"  
**\$250,000** 8/1/01-7/31/04

NIH R01 AG12423  
**\$891,501** 9/1/99-8/31/03

NIH R01 AG12423-06S1 "Transgenic *C. elegans* as amyloid disease model"  
**\$71,503** 9/1/01-8/31/02 (competitive instrumentation supplement)

NIH R01 AG12423 "Transgenic *C. elegans* as amyloid disease model"  
**\$644,067** 9/1/96-8/31/99

NSF Instrument and Laboratory Improvement Award "Undergraduate Molecular Biology Laboratory"  
**\$23,383** 1/15/90 - 1/15/92

NIH Small Instrumentation Grant  
**\$4,972** 1991

NIH FIRST award RD29HD26087 "Genetic analysis of bursal morphogenesis in *C. elegans*".  
**\$542,373** 7/1/89 - 6/30/94

## **Professional Activities**

### **Peer Review:**

(Grants) - NIH (former NOMD SRG standing member, ad hoc for CDIN, advisor for CTIP), Alzheimer's Association, TRDRP, Wellcome Trust, NSF

(Manuscripts) –*Frontiers in Genetics* (editor), *PNAS*, *Nature*, *Genomics*, *Neuroscience*, *Journal of Neuroscience*, *Journal of Molecular Biology*, *Neurobiology of Aging*, *Brain Research*, *Physiological Genomics*, *Journal of Neuropathology and Experimental Neurology*, *Experimental Biology and Medicine*, *Journal of Gerontology*, *Trends in Molecular Medicine*, *Genes & Development*

### **Memberships:**

Society for Neuroscience, Genetics Society of America, American Association for the Advancement of Science

### **Commentator:**

Alzheimer Research Forum (<http://www.alzforum.org>)

## **Publications** (reverse chronological order)

Wahl D, Smith ME, McEntee CM, Cavalier AN, Osburn SC, Burke SD, Grant RA, Nerguizian D, Lark DS, **Link CD**, LaRocca TJ. The reverse transcriptase inhibitor 3TC protects against age-related cognitive dysfunction. *Aging Cell*. 2023 Mar 22:e13798. doi: 10.1111/accel.13798. PMID: 36949552

Sharma S, Borski C, Hanson J, Garcia MA, **Link CD**, Hoeffler C, Chatterjee A, Nagpal P. Identifying an Optimal Neuroinflammation Treatment Using a Nanoligomer Discovery Engine. *ACS Chem Neurosci*. 2022 Dec 7;13(23):3247-3256. doi: 10.1021/. PMID: 36410860

Milstead RA, **Link CD**, Xu Z, Hoeffler CA. TDP-43 knockdown in mouse model of ALS leads to dsRNA deposition, gliosis, and neurodegeneration in the spinal cord. *Cereb Cortex*. 2022 Nov 28:bhac461. doi: 10.1093/cercor/bhac461. PMID: 36443249

LaRocca TJ, Cavalier AN, Roberts CM, Lemieux MR, Ramesh P, Garcia MA, **Link CD**. (2021) Amyloid beta acts synergistically as a pro-inflammatory cytokine. *Neurobiol Dis*. Nov;159:105493. doi: 10.1016/j.nbd.2021.105493. Epub 2021 Aug 28.

**Link, CD**. Is There a Brain Microbiome? *Neurosci Insights* May 27;16:26331055211018709. doi: 10.1177/26331055211018709. eCollection 2021.

Brunt VE, LaRocca TJ, Bazzoni AE, Sapinsley ZJ, Miyamoto-Ditmon J, Gioscia-Ryan RA, Neilson AP, **Link CD**, Seals DR. (2021). The gut microbiome-derived metabolite trimethylamine N-oxide modulates neuroinflammation and cognitive function with aging. *Geroscience*. Feb;43(1):377-394. doi: 10.1007/s11357-020-00257-2. Epub 2020 Aug 29. PMID: 32862276

Melnick M, Gonzales P, LaRocca TJ, Song Y, Wu J, Benatar M, Oskarsson B, Petrucelli L, Dowell RD, **Link CD**, Prudencio M. (2021) Application of a bioinformatic pipeline to RNA-seq data identifies novel virus-like sequence in human blood G3 (Bethesda). 2021 Sep 6;11(9):jkab141. doi: 10.1093/g3journal/jkab141.

LaRocca TJ, Mariani A, Watkins LR, **Link CD**. (2019) TDP-43 knockdown causes innate immune activation via protein kinase R in astrocytes. *Neurobiol Dis*. Jun 21;132:104514. doi: 10.1016

Shea D, Hsu CC, Bi TM, Paranjapye N, Childers MC, Cochran J, Tomberlin CP, Wang L, Paris D, Zonderman J, Varani G, **Link CD**, Mullan M, Daggett V. (2019)  $\alpha$ -Sheet secondary structure in amyloid  $\beta$ -peptide drives aggregation and toxicity in Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2019 Apr 30;116(18):8895-8900. doi: 10.1073/pnas.1820585116.

Melnick M, Gonzales P, Cabral J, Allen MA, Dowell RD, **Link CD**. (2019) Heat shock in *C. elegans* induces downstream of gene transcription and accumulation of double-stranded RNA. *PLoS One*. Apr 8;14(4):e0206715. doi: 10.1371/journal.pone.0206715.

Saldi TK, Gonzales PK, LaRocca TJ, **Link CD** (2019) Neurodegeneration, Heterochromatin, and Double-Stranded RNA. *J. Experimental Neuroscience* Feb 14;13:1179069519830697. doi: 10.1177/1179069519830697

Guerrero-Gómez D, Mora-Lorca JA, Sáenz-Narciso B, Naranjo-Galindo FJ, Muñoz-Lobato F, Parrado-Fernández C, Goikolea J, Cedazo-Minguez Á, **Link CD**, Neri C, Sequedo MD, Vázquez-Manrique RP, Fernández-Suárez E, Goder V, Pané R, Cabiscol E, Askjaer P, Cabello J, Miranda-Vizuete A. (2019) Loss of glutathione redox homeostasis impairs proteostasis by inhibiting autophagy-dependent protein degradation. *Cell Death Differ.* Feb 15. doi: 10.1038/s41418-018-0270-9.

Zhang YJ, Guo L, Gonzales PK, Gendron TF, Wu Y, Jansen-West K, O'Raw AD, Pickles SR, Prudencio M, Carlomagno Y, Gachechiladze MA, Ludwig C, Tian R, Chew J, DeTure M, Lin WL, Tong J, Daughrity LM, Yue M, Song Y, Andersen JW, Castanedes-Casey M, Kurti A, Datta A, Antognetti G, McCampbell A, Rademakers R, Oskarsson B, Dickson DW, Kampmann M, Ward ME, Fryer JD, **Link CD**, Shorter J, Petrucelli L. (2019) Heterochromatin anomalies and double-stranded RNA accumulation underlie *C9orf72* poly(PR) toxicity. *Science* Feb 15;363(6428). pii: eaav2606. doi: 10.1126/science.aav2606.

Julien C, Tomberlin C, Roberts CM, Akram A, Stein GH, Silverman MA, **Link CD**. (2018) In vivo induction of membrane damage by  $\beta$ -amyloid peptide oligomers. *Acta Neuropathol Commun.* Nov 29;6(1):131. doi: 10.1186/s40478-018-0634-x.

Gonzales PK, Roberts CM, Fonte V, Jacobsen C, Stein GH, **Link CD**. (2018) Transcriptome analysis of genetically matched human induced pluripotent stem cells disomic or trisomic for chromosome 21. *PLoS One.* Mar 27;13(3):e0194581. doi: 10.1371

Saldi TK, Gonzales P, Garrido-Lecca A, Dostal V, Roberts CM, Petrucelli L, **Link CD**. (2018) The *C. elegans* ortholog of TDP-43 regulates the chromatin localization of the heterochromatin protein 1 homolog, HPL-2. *Mol Cell Biol.* May 14. pii: MCB.00668-17. doi: 10.1128

Van Treeck B, Protter DSW, Matheny T, Khong A, **Link CD**, Parker R. (2018) RNA self-assembly contributes to stress granule formation and defining the stress granule transcriptome. *Proc Natl Acad Sci U S A.* 2018 Mar 13;115(11):2734-2739. doi: 10.1073/pnas.1800038115

Prudencio M, Gonzales PK, Cook CN, Gendron TF, Daughrity LM, Song Y, Ebbert MTW, van Blitterswijk M, Zhang YJ, Jansen-West K, Baker MC, DeTure M, Rademakers R, Boylan KB, Dickson DW, Petrucelli L, **Link CD**. (2017) Repetitive element transcripts are elevated in the brain of *C9orf72* ALS/FTLD patients. *Hum Mol Genet* Jun 16. Sep 1;26(17):3421-3431

Henze A, Homann T, Rohn I, Aschner M, **Link CD**, Kleuser B, Schweigert FJ, Schwerdtle T, Bornhorst J. (2016) *Caenorhabditis elegans* as a model system to study post-translational modifications of human transthyretin. *Sci Rep.* 6:37346. doi: 10.1038/srep37346.

Kramer NJ, Carlomagno Y, Zhang YJ, Almeida S, Cook CN, Gendron TF, Prudencio M, Van Blitterswijk M, Belzil V, Couthouis J, Paul JW 3rd, Goodman LD, Daugherty L, Chew J, Garrett A, Pregent L, Jansen-West K, Tabassian LJ, Rademakers R, Boylan K, Graff-Radford NR, Josephs KA, Parisi JE, Knopman DS, Petersen RC, Boeve BF, Deng N, Feng Y, Cheng TH, Dickson DW, Cohen SN, Bonini NM, **Link CD**, Gao FB, Petrucelli L, Gitler AD. (2016) Spt4 selectively regulates the expression of C9orf72 sense and antisense mutant transcripts. *Science*. 353(6300):708-12. doi:10.1126/science.aaf7791.

Munkácsy E, Khan MH, Lane RK, Borrer MB, Park JH, Bokov AF, Fisher AL, **Link CD**, Rea SL. (2016) DLK-1, SEK-3 and PMK-3 Are Required for the Life Extension Induced by Mitochondrial Bioenergetic Disruption in *C. elegans*. (2016) *PLoS Genet*. 12(7):e1006133. doi: 10.1371/journal.pgen.1006133.

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Zhang YJ, Gendron TF, Grima JC, Sasaguri H, Jansen-West K, Xu YF, Katzman RB, Gass J, Murray ME, Shinohara M, Lin WL, Garrett A, Stankowski JN, Daugherty L, Tong J, Perkerson EA, Yue M, Chew J, Castanedes-Casey M, Kurti A, Wang ZS, Liesinger AM, Baker JD, Jiang J, Lagier-Tourenne C, Edbauer D, Cleveland DW, Rademakers R, Boylan KB, Bu G, **Link CD**, Dickey CA, Rothstein JD, Dickson DW, Fryer JD, Petrucelli L. (2016) C9ORF72 poly(GA) aggregates sequester and impair HR23 and nucleocytoplasmic transport proteins. *Nature Neuroscience* 19(5):668-677

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Saldi TK, Ash PEA, Wilson G, Gonzales P, Garrido-Lecca A, Roberts CM, Dostal V, Gendron TF, Stein LD, Blumenthal T, Petrucelli L, **Link CD**. (2014) TDP-1, the *C. elegans* ortholog of TDP-43, limits the accumulation of double-stranded RNA. *EMBO J* Dec 17;33(24):2947-66.

Hassan WM, Dostal V, Yerg JE, **Link CD**. Identifying A $\beta$ -specific pathogenic mechanisms using a nematode model of Alzheimer's disease. (2014) *Neurobiology of Aging* Feb;36(2):857-66.

Machino K, **Link CD**, Wang S, Murakami H, Murakami S. (2014) A semi-automated motion-tracking analysis of locomotion speed in the *C. elegans* transgenics overexpressing beta-amyloid in neurons. *Front Genet*. Jul 4;5:202. doi: 10.3389

Muñoz-Lobato F, Rodríguez-Palero MJ, Naranjo-Galindo FJ, Shepard F, Gaffney CJ, Szweczyk NJ, Hamamichi S, Caldwell KA, Caldwell GA, **Link CD**, Miranda-Vizuete A. (2013) Protective role of DNJ-27/ERdj5 in *Caenorhabditis elegans* models of human neurodegenerative diseases. *Antioxid Redox Signal*. Jan 10;20(2):217-35.

Lublin, AL and Link, CD. Alzheimer's disease drug discovery: in vivo screening using *Caenorhabditis elegans* as a model for  $\beta$ -amyloid peptide-induced toxicity. (2013) *Drug Discov Today Technol.* Spring;10(1):e115-9. doi: 10.1016/j.ddtec.2012.02.002

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Cacho-Valadez B, Muñoz-Lobato F, Pedrajas JR, Cabello J, Fierro-González JC, Navas P, Swoboda P, **Link C. D**, Miranda-Vizueté A. (2012) The characterization of the *Caenorhabditis elegans* mitochondrial thioredoxin system uncovers an unexpected protective role of thioredoxin reductase 2 in  $\beta$ -amyloid peptide toxicity. *Antioxid Redox Signal.* Jun 15;16(12):1384-400.

**Link C. D**, Saldi T. K. Cell death by glutamine repeats? (2012) *Science.* Feb 24;335(6071):926-7.

Cotella D, Hernandez-Enriquez B, Wu X, Li R, Pan Z, Leveille J, **Link C.D.**, Oddo S, Sesti F. (2012) Toxic role of K<sup>+</sup> channel oxidation in mammalian brain. *J Neurosci.* Mar 21;32(12):4133-44

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Mendenhall A.R., Wu D., Park S.K., Cypser JR, Tedesco PM, **Link C.D.**, Phillips P.C., Johnson T.E. (2011) Genetic dissection of late-life fertility in *Caenorhabditis elegans*. *J Gerontol A Biol Sci Med Sci.* Aug;66(8):842-54.

McColl, G., Rogers, A.N., Alavez, S., Hubbard, A.E., Melov, S., **Link, C.D.**, Bush, A.I., Kapahi, P., Lithgow, G.J. (2010) Insulin-like Signaling Determines Survival during Stress via Posttranscriptional Mechanisms in *C. elegans*. *Cell Metab*;12(3):260-72.

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Dostal, V. and **Link C.D.** (2010) Assaying  $\beta$ -amyloid toxicity using a transgenic *C. elegans* model. *J Vis Exp.* Oct 9;(44).

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Hassan, W. M., Merin, D. A., Fonte V., **Link, C. D.** (2009) AIP-1 ameliorates  $\beta$ -amyloid peptide toxicity in a *Caenorhabditis elegans* Alzheimer's disease model. *Hum Mol Genet.* Aug 1;18(15):2739-47.

Zhang, Y. J., Xu Y. .F, Cook, C., Gendron, T. F., Roettges, P., **Link, C. D.**, Lin, W. L., Tong, J., Castanedes-Casey, M., Ash, P., Gass, J., Rangachari, V., Buratti, E., Baralle, F., Golde, T. E., Dickson, D. W., Petrucelli, L. (2009) Aberrant cleavage of TDP-43 enhances aggregation and cellular toxicity. *Proc Natl Acad Sci U S A.* May 5;106(18):7607-12.

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