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| NAME**James Shorter, Ph.D.** | POSITION TITLE**Professor of Biochemistry and Biophysics** |
| eRA COMMONS USER NAME (credential, e.g., agency login)**SHORTERJ** |
| EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)* |
| INSTITUTION AND LOCATION | DEGREE*(if applicable)* | MM/YY | FIELD OF STUDY |
| Keble College, University of Oxford, U.K. | B.A., M.A. | 10/92-05/95 | Biology |
| Imperial Cancer Research Fund, University College London, University of London, U.K. (Professor Graham Warren) | Ph.D. | 09/95-05/00 | Cell Biology |
| Yale University School of Medicine, New Haven CT. (Professor Graham Warren) | Post-Doc | 05/00-05/02 | Biochemistry |
| Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge, MA. (Professor Susan Lindquist) | Post-Doc | 07/02-07/05 | Biochemistry/Genetics |

**A. Personal Statement**

I am a Professor of Biochemistry and Biophysics at the Perelman School of Medicine at the University of Pennsylvania. My research program aims to elucidate how to therapeutically counter deleterious protein misfolding in neurodegenerative diseases such as ALS/FTD, synucleinopathies, Alzheimer’s disease, and Alzheimer’s Disease-Related Dementias (ADRDs). We have been recognized by several prestigious awards, including: NIH Director’s New Innovator Award, Ellison Medical Foundation New Scholar in Aging Award, Bill and Melinda Gates Grand Challenges Explorations Award, Linda Pechenik Montague Investigator Award, Sanofi Innovation Award, two Department of Defense Therapeutic Idea Awards, and the Michael S. Brown New Investigator Award, which recognizes faculty engaged in innovative discoveries.

We have a long-standing interest in the function and mechanism of protein disaggregases. My group discovered that Hsp104, a powerful protein disaggregase from yeast, can dissolve diverse amyloid conformers and toxic soluble oligomers formed by several disease proteins, including amyloid-, tau, polyglutamine, and -synuclein (DeSantis et al. *Cell*. 2012. 151(4):778-793). We have pioneered the engineering of Hsp104 to have enhanced activity against TDP-43, FUS, and -synuclein (Jackrel et al., *Cell*. 2014. 156(1-2):170–182). We have also discovered several human protein disaggregases, including Hsp110/Hsp70/Hsp40 (Shorter, *PLoS ONE*. 6:e26319), Skd3 (Cupo and Shorter, *eLife*. 2022. 9:e55279), and nuclear-import receptors (Guo et al. *Cell*. 2018. 173(3):677-692). Importantly, nuclear-import receptors (NIRs) can reverse aberrant phase transitions of ALS/FTD-linked RNA-binding proteins with prion-like domains (Guo et al. *Cell*. 2018. 173(3):677-692). Thus, Karyopherin-b2 (Kapb2) reverses FUS fibrillization, whereas importin-a and Karyopherin-b1 reverse TDP-43 fibrillization (Guo et al. *Cell*. 2018. 173(3):677-692). I have a strong record in the successful training and mentoring of graduate students. I have graduated ten Ph.D. students since launching my group with three more in training. I strive to promote an inclusive and supportive scientific research environment in my lab. We focus on training sound experimental design coupled to rigorous statistical and quantitative approaches. I am very supportive of trainees’ participation in activities required to enable a facile and timely transition into careers in the biomedical research workforce and beyond.

Ongoing projects that I would like to highlight include:

R01GM099836. (PI: Shorter). 12/01/2012-05/31/2025.

NIGMS R01. *Defining mechanisms of AAA+ disaggregases*.

Research Grant. (PI: Shorter). 07/01/2019-06/30/2022.

The G. Harold & Leila Y. Mathers Foundation. *Enhancing human protein disaggregases to counter aging and neurodegenerative disease.*

R21AG065854.(PI: Shorter). 01/10/2020-12/31/2022.

NIA R21. *Programming Human-Disaggregase Systems Against FTD.*

20-IIA-534. (PI: Shorter). 12/01/2019-02/28/2023.

ALS Association. *Antagonizing neurotoxic phase transitions of TDP-43 and FUS with small RNA therapeutics*.

Target ALS Consortium. (PI: Shorter). 05/15/2020-12/31/2022.

Target ALS. *Identification of Small Molecule Inhibitors of TDP-43 Liquid-Liquid Phase Separation.*

W81XWH-20-1-0242. Therapeutic Idea Award. (PI: Shorter). 07/01/2020-06/30/2022.

Department of Defense, ALS Research Program. *Antagonizing neurotoxic phase transitions of TDP-43 and FUS with small RNA therapeutics*.

R01GM138690. (PI: Southworth. Co-Investigator: Shorter). 04/01/2021–03/31/2025.

NIGMS R01. *Mechanisms of Protein Disaggregation and Turnover by AAA+ Chaperones.*

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

Positions and Scientific Appointments:

**1. ∫**2022-present: Scientific Advisory Board, Confluence Therapeutics.

**2.** 2021-present: Consultant, Neumora.

**3.** 2021-present: Consultant, ADRx.

**4.** 2021-present: Consultant, Korro Bio.

**5.** 2021-2022: Scientific Advisory Board, Vivid Sciences.

**6.** 2020-2021: Consultant, Maze Therapeutics.

**7.** 2020-present: Scientific Advisory Board, Dewpoint Therapeutics.

**8.** 2018-present: Professor, University of Pennsylvania, Philadelphia, PA.

**9.** 2013-2018: Associate Professor, University of Pennsylvania, Philadelphia, PA.

**10.** 2007-2013: Assistant Professor, University of Pennsylvania, Philadelphia, PA.

**11.** 2005-2007:Senior Research Associate, Whitehead Institute for Biomedical Research, MIT, Cambridge, MA.

Honors: The G. Harold & Leila Y. Mathers Foundation Research Award (2019); Cecile M. Pickart Memorial Lecture, Department of Biochemistry and Molecular Biology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (2018); Department of Defense Therapeutic Idea Award (2017, 2020); Sanofi Innovation Award (2017); Linda Pechenik Montague Investigator Award (2014-2016); Target ALS Consortium Leader (2014-2016); ALS Association Investigator Initiated Award (2014-present); Muscular Dystrophy Association Research Grant Award (2013-2016); Target ALS PI (2013-present); Michael S. Brown New Investigator Research Award (2012); Robert Packard Center for ALS Research PI (2010-present); Bill and Melinda Gates Foundation Grand Challenges Explorations Award (2010-2011); Ellison Medical Foundation New Scholar in Aging Award (2009-2013); NIH Director’s New Innovator Award (2007-2012); American Heart Association National Scientist Development Award (2005-2009); Charles A. King Trust Postdoctoral Fellowship (2003-2005); Pontecorvo Prize for best Ph.D. thesis at ICRF (2001); Imperial Cancer Research Fund (ICRF) Predoctoral Fellowship (1995-2000); Keble Scholar Award (1993-1995).

Selected Invited Seminars (last 3 years): TSRC Workshop on Phase Separation in Biology and Disease, Telluride, CO (2022).; Symposium on Structural Biology 2021 (SimBE 2021), Rio, Brazil (2021); Cell Symposium on Biological Assemblies, Cell Press, Cambridge, MA (2021); Dept. of Chemistry, Villanova University, Villanova, PA (2021); Cellular and Protein Homeostasis Webinar Series, University of Lausanne, Switzerland (2021); Molecular & Cell Biology & Genetics Seminar Series, Drexel College of Medicine, Philadelphia, PA (2021); UCL Queen Square Motor Neuron Disease Centre, UCL, London, U.K. (2021); Neumora, Cambridge, MA (2021); FASEB Virtual Meeting 'Protein Aggregation Conference: Function, Dysfunction, and Disease' (2021); Middle Atlantic Regional Meeting of the American Chemical Society, University of Delaware, Newark, DE (2021); SickKids, The University of Toronto, Ontario, Canada (2021); Advances in Biomedical Research Seminar Series, University of Ottawa, Ottawa, Ontario, Canada (2021); Department of Pharmacology & Experimental Therapeutics, Boston University, Boston, MA (2021); Keynote seminar, CReATe Consortium Annual Meeting, University of Miami, Miami, FL (2021); Interdisciplinary Research Center on Biology and Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China (2021); Department of Biochemistry, West Virginia University, Morgantown, WV (2021); Biophysics of Amyloid Formation, Ulm University, Ulm, Germany (2021); Faze Medicines, Cambridge, MA (2020); Institute for Quantitative Biomedicine, Rutgers University, New Brunswick, NJ (2020); RNA at the Bench and Bedside II Virtual Conference, Nature Conferences (2020); Florida Atlantic University Brain Institute, Boca Raton, FL (2020); Proteostasis Consortium Seminar, Northwestern University, Evanston, IL (2020); Cell & Molecular Biology Seminar Series, St. Jude Children’s Research Hospital, Memphis, TN (2020); Keystone Symposium: AAA+ proteins from atomic structures to organisms, Lake Tahoe, CA (2020); Dementia Discovery Fund, Boston, MA (2020); Dewpoint Therapeutics, Boston, MA (2020); Keynote Lecture, Amyotrophic Lateral Sclerosis and Related Motor Neuron Diseases Gordon Research Seminar, Mount Snow, VT (2019); Dept. of Chemistry & Biochemistry, University of Toledo, Toledo, OH (2019); 64th Annual Meeting of the Biophysical Society, Baltimore, MD (2019); AFTD Workshop on TDP-43 biomarkers, Miami, FL (2019); Dept. of Pathology and Laboratory Medicine Grand Rounds, University of Pennsylvania, Philadelphia, PA (2019); Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA (2019); Target ALS Annual Meeting, Cambridge, MA (2019, 2021, 2022); Packard Center Annual Symposium, Baltimore, MD (2019, 2021, 2022);

Grant review panels: NINDS Board of Scientific Counselors (2021, ad hoc); MRC UK Dementia Research Institute Review (2021); NIH Drug Discovery for the Nervous System (DDNS) Study Section Member (2019-present); NIH-NIGMS-K99 peer-review (2018); W.M. Keck Foundation (2018); Paul G. Allen Frontiers Group (2018); Chan Zuckerberg Initiative Neurodegeneration Challenge Network (2018); Alzheimer’s Research UK (2018); Human Frontiers Science Program (2015); ALS Association (2015, 2016, 2019, 2021); NIH Membrane Biology and Protein Processing (MBPP) Study Section (2015); Fondation pour la Recherche Médicale (2014); Israel Science Foundation (2014, 2016); ATIP-Avenir Program (2014); Wellcome Trust (2014); European Research Council (2012); Swiss National Science Foundation (2012); L’Agence Nationale de la Recherche (2011); Netherlands Organization for Health Research and Development (2011); Peer Reviewed Medical Research Program, Department of Defense. (2011; 2020); NIH Special Emphasis Panel/Scientific Review Group ZAI1 BLG-M (2011); Division of Molecular and Cellular Biosciences, NSF (2010, 2016).

Editorial service: Editorial board, *Dis. Mod. Mech.* (2017-present); Editorial board, *Journal of Biological Chemistry* (2016-present); Editor, *Biophysical Journal* (2016-present); Associate Editor, *Frontiers in Molecular Biosciences (Protein Folding, Misfolding & Degradation)* (2014-present); Editorial advisory panel, *Biochemical Journal* (2007-present).

Professional Memberships: American Society for Cell Biology; Biochemical Society; Biophysical Society; Protein Society; American Society for Biochemistry and Molecular Biology; American Chemical Society; American Society for Microbiology; Society for Neuroscience.

**C. Contribution to Science**

***C.1. Summary of Career Publications***

**Total publications:** 172 **Total citations:** 18,849 (April 2022, Google Scholar)

**h-index:** 66 (66 publications have at least 66 citations, April 2022, Google Scholar)

Complete list (MyBibliography): <http://www.ncbi.nlm.nih.gov/sites/myncbi/james.shorter.1/bibliography/44799634/public/?sort=date&direction=descending>.

***C.2.* *Mechanisms and engineering of Hsp104, a prion disaggregase***. We have elucidated and pioneered mechanisms by which the hexameric AAA+ protein, Hsp104, functions as a prion disaggregase. We have also engineered potentiated variants of Hsp104 to combat neurodegenerative disease. We have generated potentiated Hsp104 variants that reverse the aggregation and toxicity of TDP-43, FUS, TAF15, and -synuclein, which are implicated in several neurodegenerative diseases.

a. DeSantis, M.E., E.H. Leung, E.A. Sweeny, M.E. Jackrel, M. Cushman-Nick, A. Neuhaus-Follini, S. Vashist, M.A. Sochor, M.N. Knight, and **J. Shorter^**. (2012). Operational Plasticity Enables Hsp104 to Disaggregate Diverse Amyloid and Nonamyloid Clients. Cell. 151(4):778-793. **(^Corresponding author)**. PMCID: PMC3496281

b. Jackrel, M.E., M.E. DeSantis, B.A. Martinez, L.M. Castellano, R.M. Stewart, K.A. Caldwell, G.A. Caldwell, and **J. Shorter^**. (2014). Potentiated Hsp104 variants antagonize diverse proteotoxic misfolding events. *Cell*. 156(1-2):170–182. **(^Corresponding author)**. PMCID: PMC3909490

c. Gates, S.N\*., A.L. Yokom\*, J. Lin, M.E. Jackrel, A.N. Rizo, N.M. Kendsersky, C.E. Buell, E.A. Sweeny, K.L. Mack, E. Chuang, M.P. Torrente, M. Su, **J. Shorter**, and D.R. Southworth. (2017). Ratchet-like polypeptide translocation mechanism of the AAA+ disaggregase Hsp104. *Science*. 357(6348):273-279. (\*Co-first author). PMCID: PMC5770238

d. Tariq, A.\*, J. Lin\*, M.E. Jackrel\*, C.D. Hesketh, P.J. Carman, K.L. Mack, R. Weitzman, C. Gambogi, O.A. Hernandez Murillo, E.A. Sweeny, E. Gurpinar, A.L. Yokom, S.N. Gates, K. Yee, S. Sudesh, J. Stillman, A.N. Rizo, D.R. Southworth, and **J. Shorter^**. (2019). Mining disaggregase sequence space to safely counter TDP-43, FUS, and alpha-synuclein proteotoxicity. *Cell Rep.* 28(8):2080–2095. **(^Corresponding author)**. PMCID: PMC6750954

***C.3. Discovery and dissection of the metazoan protein-disaggregase machinery*.** Hsp104 is highly conserved in eubacteria and eukaryotes but an exact ortholog is surprisingly absent from metazoa (animals). Thus, whether animal cells renature large protein aggregates had long remained unclear. We have established that human Hsp110, Hsp70, Hsp40, and small heat shock proteins synergize to dissolve disordered aggregates and can also depolymerize amyloid fibrils from their ends. We have also found that Skd3 (human ClpB) is a potent mitochondrial protein disaggregase. We have also uncovered human TRIM11 and DAXX as potent, ATP-independent protein disaggregases. Finally, we have also discovered that human nuclear-import receptors can disaggregate their specific cargo, including FUS and TDP-43.

a. **Shorter, J^**. (2011). The mammalian disaggregase machinery: Hsp110 synergizes with Hsp70 and Hsp40 to catalyze protein disaggregation and reactivation in a cell-free system. *PLoS ONE*. 6(10):e26319. **(^Corresponding author).** PMCID: PMC3194798

b. Duennwald, M.L., A.L. Echeverria, and **J. Shorter^**. (2012). Small heat shock proteins potentiate amyloid dissolution by protein disaggregases from yeast and humans. PLoS Biol. 9(6):e1001346. **(^Corresponding author)**. PMCID: PMC3378601

c. Guo, L.\*, H.J. Kim\*, H. Wang\*, J. Monaghan°, F. Freyermuth°, J.C. Sung°, K. O’Donovan, C.M. Fare, Z. Diaz, N. Singh, Z.C. Zhang, M. Coughlin, E.A. Sweeny, M.E. DeSantis, M.E. Jackrel, C.B. Rodell, J.A. Burdick, O.D. King, A.D. Gitler, C. Lagier-Tourenne, U.B. Pandey, Y.M. Chook, J.P. Taylor^, and **J. Shorter^**. (2018). Nuclear-import receptors reverse aberrant phase transitions of RNA-binding proteins with prion-like domains. *Cell*. 173(3):677-692. (\*Co-first author. °Co-second author. **^Co-corresponding author**). PMCID: PMC5911940

d. Cupo, R.R., and **J. Shorter^**. (2020). Skd3 (human CLPB) is a potent mitochondrial protein disaggregase that is inactivated by 3-methylglutaconic aciduria-linked mutations. eLife. 9:e55279 **(^Corresponding author)**. PMCID: PMC7343390

***C.4. RNA-binding proteins with prion-like domains underlie neurodegenerative disease***. Yeast prion proteins (e.g. Sup35) harbor a distinctive ‘prion domain’ enriched in asparagine, glutamine, tyrosine, and glycine, which confers prion behavior and can even be scrambled and maintain prionogenicity. Thus, amino-acid composition rather than primary sequence can enable prionogenesis. We have scoured the human genome with an algorithm that detects domains with this unusual amino-acid composition and uncovered ~250 proteins with ‘prion-like’ domains (PrLDs). Among these prion candidates, RNA-binding proteins (RBPs) were enriched, including TDP-43 and FUS, which misfold and cause ALS/FTD. We hypothesized that additional RBPs with PrLDs would underpin neurodegenerative disease and subsequently connected TAF15, EWSR1, hnRNPA1, and hnRNPA2 mutations and pathology to ALS/FTD. We have recently discovered that short RNAs and PARP inhibitors can antagonize the aberrant phase separation of TDP-43. We have also discovered that poly(GR) accelerates TDP-43 aggregation.

a. Kim\*, H.J., N.C.Kim\*, Y.D. Wang\*, E.A. Scarborough\*, J. Moore\*, Z. Diaz\*, K.S. MacLea, B. Freibaum, S. Li, A. Molliex, A.P. Kanagaraj, R. Carter, K.B. Boylan, A.M. Wojtas, R. Rademakers, J.L. Pinkus, S.A. Greenberg, J.Q. Trojanowski, B.J. Traynor, B.N. Smith, S. Topp, A.S. Gkazi, J. Miller, C.E. Shaw, M. Kottlors, J. Kirschner, A. Pestronk, Y.R. Li, A.F. Ford, A.D. Gitler, M. Benatar, O.D. King, V.E. Kimonis, E.D. Ross, C.C. Weihl, **J. Shorter^**, and J.P. Taylor^. (2013). Mutations in prion-like domains in hnRNPA2B1 and hnRNPA1 cause multisystem proteinopathy and ALS. *Nature*. 495(7442):467–473. **(\*Co-first author. ^Co-corresponding author)**. PMCID: PMC3756911

b. Mann, J.R., A.M. Gleixner, J.C. Mauna, E. Gomes, M.R. DeChellis-Marks, P.G. Needham, K.E. Copley, B. Hurtle, B. Portz, N.J. Pyles, L. Guo, C.B. Calder, Z.P. Wills, U.B. Pandey, J.K. Kofler, J.L. Brodsky, A. Thathiah, **J. Shorter**, and C.J. Donnelly. (2019). RNA binding antagonizes neurotoxic phase transitions of TDP-43. *Neuron.* 102(2):321-338.e8. PMCID: PMC6472983

c. McGurk L., E. Gomes, L. Guo, J. Mojsilovic-Petrovic, V. Tran, R.G. Kalb, **J. Shorter^**, and N.M. Bonini^. (2018). Poly(ADP-ribose) prevents aberrant phase separation of TDP-43 by promoting liquid demixing and stress-granule localization. *Mol. Cell.* 71(5):703-717. **(^Co-corresponding author)**. PMCID: PMC6128762

d. Cook, C.N.\*, Y. Wu\*, H.M. Odeh\*, T.F. Gendron, K. Jansen-West, G. del Rosso, M. Yue, P. Jiang, E. Gomes, J. Tong, L.M. Daughrity, N.M. Avendano, M. Castanedes-Casey, W. Shao, B. Oskarsson, G.S. Tomassy, A. McCampbell, F. Rigo, D.W. Dickson, **J. Shorter^**, Y-J. Zhang^, and L. Petrucelli^. (2020). C9orf72 poly(GR) aggregation induces TDP-43 proteinopathy. *Sci. Transl. Med.* 12(559):eabb3774. **(\*Co-first author. ^Co-corresponding author**). PMCID: PMC7989020.

***C.5. Small-molecule drugs and protein disaggregases can drive prion-strain selection.*** Prions can assemble into an ensemble of different self-replicating structures, termed strains. Each strain confers a distinct phenotype and self-replicates at different rates depending on the environment. As replicators, prions are units of selection. Thus, natural selection inescapably enriches or depletes various prion strains from populations depending on their conformational fitness (ability to self-replicate) in the prevailing environment. We were the first to establish that small-molecule drugs and protein disaggregases can drive prion-strain selection events. Importantly, we have isolated synergistic small-molecule combinations that counter prion diversity by eliminating multiple prion strains. Our findings suggest that combination therapies might hold promise for treating amyloid and prion disorders.

a. Roberts, B.E., M.L. Duennwald^, H. Wang, C. Chung, N.P. Lopreiato, E.A. Sweeny, M.N. Knight, and **J. Shorter^**. (2009). A synergistic small-molecule combination directly eradicates diverse prion strain structures. Nat. Chem. Biol. 5(12):936-946. **(^Co-Corresponding author)**. PMCID: PMC2909773

**b. Shorter, J.^** (2010). Emergence and natural selection of drug-resistant prions. Mol. Biosyst. 6(7):1115-1130. **(^Corresponding author)**. PMCID: PMC2936920

c. Duennwald, M.L.^, and **J. Shorter^**. (2010). Countering amyloid polymorphism and drug resistance with minimal drug cocktails. Prion. 4(4): 244-251. **(^Co-Corresponding author)**. PMCID: PMC3268956

d. DeSantis, M.E., and **J. Shorter^**. (2012). Hsp104 Drives ''Protein-Only'' Positive Selection of Sup35 Prion Strains Encoding Strong [PSI+]. Chemistry & Biology. 19(11):1400-1410. **(^Corresponding author)**. PMCID: PMC3508465