COURTNEY L. THAXTON

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EDUCATION

The University of Central Florida, Graduate School of Biomolecular Sciences, Orlando, FL
Doctor of Philosophy, Biomolecular Sciences; Emphasis: Cell Signaling, November 2007.
Dissertation: "*Mechanisms promoting phosphorylation of the NF2 tumor suppressor and its effects on Schwann cell development*."

The University of Central Florida, Orlando, FL
Bachelor of Science, Molecular Biology and Microbiology, May 2002

PROFESSIONAL EXPERIENCE

The University of North Carolina, Chapel Hill, NC **2008—Present**

Assistant Director (Jan 2019-present)
Advisor: Jonathan S. Berg, M.D., Ph.D., Professor
Overseeing the day-to-day operation of the UNC ClinGen Biocuration and Coordination Core, including assisting with the supervision, oversight, and training of 10+ member of the Core, and that of the undergraduate pipeline that contributes anywhere from 2-6 additional volunteers. Generating, coordinating, and editing quarterly, half yearly and yearly milestone and progress reports to granting agency (NHGRI-NIH). HR related tasks, including posting, interviewing, and hiring of new employees, and annual reviews of existing employees.

Biocurator (2016-present)
Advisor: Jonathan S. Berg, M.D., Ph.D., Professor
Classifying and scoring gene:disease relationships by evaluating the strength of evidence presented in literature and using a newly developed metric framework for the Clinical Genome Resource (ClinGen). Leading a working group comprised of biocurators, clinicians and scientists to assess lumping and splitting of disease entities for curation, and creating guidelines for its implementation. Participate in education and training of biocurators and the development of modules, procedures, and guidelines for future curation training. Integral member of the Data Platform working group that devises strategies to improve curation efficiency and workflows with the development and/or enhancement of software platforms. Software liaison responsible for design and testing of new software platforms that involve metric reporting and tracking of curations, as well as a database to track the training and efforts of community curators.

Postdoctoral Research Associate (2012—2016)
Advisor: Benjamin Philpot, Ph.D., Professor
Investigating the molecular mechanisms regulating transcription factor 4, *Tcf4*, in the nervous system, and how mutation of *Tcf4* results in the neurodevelopmental, autism associated disorder, Pitt-Hopkins syndrome (PTHS). Generated two novel mouse models of PTHS; (1) a pathogenic point mutation model harboring the most recurring mutation in PTHS (human R580W, mouse R579W), and (2) a deletion model that lacks three out of four causative arginines associated with PTHS (*Tcf4*$^{\triangle 574\text{-}579}$).

Postdoctoral Research Fellow (2008—2012)
Advisor: Manzoor Bhat, Ph.D., M.S., Professor
Studied the role of *Neurofascin* (*Nfasc*) in axonal domain organization, and specifically how the neuronal isoform of *Nfasc* regulated the formation, stability and maintenance of the Node of Ranvier.

The University of Central Florida, Orlando, FL **2002—2007**
Doctoral Research (2003—2007)
Advisor: Cristina Fernandez-Valle, Ph.D., Professor
Examined how phosphorylation modulates the function of the Neurofibromatosis type II (NF2) tumor suppressor Merlin, and how these changes affect Schwann cell development.

Master's Research (2002—2003) **2002—2003**
Advisor: Roseanne White, Ph.D., Professor
Investigated the role of grass pollen from *Paspalam Notatum* (Bahia-grass) in the immune response. The majority of my work centered on isolating and purifying several samples of different grass species.

Non-Research Position/ Sales, Orlando, FL **1997—2002**
Assistant Manager/ Lead
Company/Owners: Lomac Inc., John and Lori MacQueen
Responsible for supervising, training and overseeing day-to-day operations for a small business with booths in Universal Studios, Sea World, and Disney Resorts.

HONORS/AWARDS

The University of North Carolina:

Outstanding Contributions to genomic medicine (Berg lab), inaugural receipient	2017
Service Award (teaching RCR ethics course), UNC	2014
Brain Behavior Research Foundation (formerly NARSAD) Young Investigator Grant	2014—2016
Research Ethics Certification, UNC	2012
NIH Ruth L. Kirschstein Postdoctoral NRSA Fellowship	2011—2012
National Multiple Sclerosis Society Postdoctoral Fellowship (declined due to NIH NRSA)	2011
Postdoctoral Award for Research Excellence (PARE), UNC	2010
Best Postdoctoral Presentation, Cell and Molecular Physiology Research Day, UNC	2009

The University of Central Florida:

Mentoring in Science Award, Lake Highland Prep ASPIRE program	2004
Dean's List	1998—1999
Florida Bright Futures Scholarship	1998—2002

TEACHING EXPERIENCE

The University of North Carolina 2012—2014
Instructor
RCR Ethics Course (graduate course): Patrick Brandt (coordinator), Donita Robinson, Ph.D. (Co-Instructor).

The University of Central Florida 2002—2004
Graduate Teaching Assistant

Honors Quantitative Methods Lab (Fall 2003 and Spring 2004). PI: Ratna, Chakrabarti, Ph.D.
Quantitative Biological Methods Lab (Fall 2002, Spring 2003, Fall 2003, Spring 2004). PI: Roseanne White and Ratna Chakrabarti, Ph.D. Responsible for teaching standard laboratory methods to undergraduates.

PUBLICATIONS

Articles in submission (or press):

Robinson, P.N., Ravanmehr, V., Jacobsen, J.O.B., Danis, D. Zhang, A., Carmody, L.C., Gargano, M., **Thaxton, C**., UNC Biocuration Core, Reese, J., Holtgrewe, M., Kohler, S, McMurry, J., Haendel, M., Smedley, D. (***in submission, Nov 2019***). Interpretable Clinical Genomics with a Likelihood Ratio Paradigm. Medriv link: https://www.medrxiv.org/content/10.1101/2020.01.25.19014803v1

Refereed Articles:

Phan, B.D., Bohlen, J. F., Davis, B. A., Zengou, Y., Chen H.y., Mayfield, B. Rao, S., Page, S., Campbell, M., Smith, H., Gallop, D., Kim, H., **Thaxton, C.,** Simon, J., Burke, E., Shin, J.H., Kennedy, A., Sweatt, J.D., Philpot, B.D., Jaffe, A.D., Maher, B.J. (2020). A myelin-related transcriptomic profile is shared by Pitt-Hopkins syndrome models and human autism spectrum disorder. *Nat Neurosci.* 2020 Mar;23(3):375-385. doi: 10.1038/s41593-019-0578-x. PMID: 32015540

Haendel, M., Vasilevsky, N., Unni, D., Bologa, C., Harris, N., Rehm, H., Hamosh, A., Baynam, G., Groza, T., McMurry, J., Dawkins, H., Rath, A., **Thaxon, C.**, Bocci, G., Joachimiak, M.P., Köhler, S., Robinson, P.N., Mungall , C., Oprea, T.I. (2019). How many rare diseases are there? *Nar Rev Drug Dis.* Comment 5 Dec 2019. doi: 10.1038/d41573-019-00180-y. URL: https://www.nature.com/articles/d41573-019-00180-y

Ingles, J., Goldstein, J., **Thaxton, C.,** Caleshu, C., Corty, E.W., Crowley, S.B., Dougherty, K., Harrison, S.M., McGlaughon, J., Milko, L.V., Morales, A., Seifert, B., Strande, N., Thomson, K., van Tintelen, J.P., Wallace, K., Walsh, R., Wells, Q. Whiffin, N., Witkowski, L. Semsarian, C., Ware, J.S., Hershberger, R.E.,* Funke, B.*. (2019) Evaluating the Clinical Validity of Hypertrophic Cardiomyopathy Genes. *Circ Genom Precis Med.* Feb; 12(2): e002460. doi: 10.1161/CIRCGEN.119.002460. PMID: 30681346

McGlaughon, J.L., Goldstein, J.L., **Thaxton, C.**, Hemphill, S.E., Berg, J.S. (2018) The progression of the ClinGen gene clinical validity classification over time. *Hum Mutat*. Nov;39(11):1494-1504. doi: 10.1002/humu.23604. PMID: 30311372

Helbig, I., Riggs, E.R., Barry, C.A., Klein, K.M., Dyment, D., **Thaxton, C.**, Sadikovic, B., Sands, T.T., Wagnon, J.L., Liaquat, K., Cilio, M.R., Mirzaa, G., Park, K., Axeen, E., Butler, E., Bardakjian, T.M., Striano, P., Poduri, A., Siegert, R.K., Grant, A.R., Helbig, K.L., Mefford, H.C. (2018) The ClinGen Epilepsy Gene Curation Expert Panel-Bridging the divide between clinical domain knowledge and formal gene curation criteria. *Hum Mutat*. Nov;39(11):1476-1484. doi: 10.1002/humu.23632. PMID: 30311377

Thaxton, C.*, Kloth A.D.*, Clark E.P., Moy, S.S., Chitwood, R.A., Philpot, B.D. (2018). Common Pathophysiology in Multiple Mouse Models of Pitt-Hopkins Syndrome. *J Neurosci.* 38(4):918-936. PMID: 29222403. * co-authors

Judson, M.C., Burette, A.C[*], **Thaxton, C.L.**[*], Pribisko, A.L., Shen, M.D. Rumple, A.M., Del Cid, W.A., Paniagua, B. Styner, M., Weinberg, R.J., Philpot, B.D. (2017). Decreased axon caliber underlies loss of fiber tract integrity, disproportional reductions in white matter volume, and microcephaly in Angelman syndrome model mice. PMID: 28663201 *** co-authors**

Thaxton, C., Bott M., Walker B., Sparrow N.A., Lambert S., Fernandez-Valle C. (2011). Schwannomin/merlin promotes Schwann cell elongation and influences myelin segment length. *Mol Cell Neurosci* 47(1):1-9. PMID: 21182951

Thaxton, C., Pillai, A.M., Pribisko, A.L., Dupree, J.L., Bhat, M.A. (2011). Nodes of Ranvier act as barriers to restrict invasion of the flanking paranodal domains in myelinated axons. *Neuron* 69(2): 244-57. PMID: 21262464

Thaxton, C., Pillai, A.M., Pribisko, A.L., Labasque, M., Dupree, J.L., Faivre-Sarrailh, C., Bhat, M.A. (2010). In vivo deletion of Immunoglobulin domains 5-6 in Neurofascin (Nfasc) reveals domain specific requirements in myelinated axons. *J Neurosci* 30 (14): 4868-76. PMID: 20371806

Pillai, A.M., **Thaxton, C.**, Pribisko, A.L., Cheng, J.G., Dupree, J.L., Bhat, M.A. (2009) Spatiotemporal ablation of myelinating glia-specific neurofascin (Nfasc(NF155)) in mice reveals gradual loss of axoglial junctions and concomitant disorganization of axonal domains. *J Neurosci Res* 87 (8): 1773-93. PMID: 19185024

Thaxton, C., Lopera, J., Bott, M., Fernandez-Valle, C. (2008). Neuregulin and laminin stimulate phosphorylation of the NF2 tumor suppressor in Schwann cells by distinct protein kinase A and p21-activated kinase dependent pathways. *Oncogene* 27(19): 2705-15. PMID: 17998937

Thaxton, C., Lopera, J., Bott, M., Baldwin, M.E., Kalidas, P., Fernandez-Valle, C. (2007) Phosphorylation of the NF2 tumor suppressor in Schwann cells is mediated by Cdc42-Pak and requires paxillin binding. *Mol Cell Neurosci* 34(2): 231-42. PMID: 17175165

Review Articles:

Buttermore, E.D., **Thaxton, C.L.**, Bhat, M.A. (2013). Organization and Maintenance of Molecular Domains in Myelinated Axons. *J Neurosci Res*. 91(5): 603-22. PMID: 23404451

Book Chapter(s):

Thaxton, C. and Bhat, M.A. (2009). Myelination and Regional Domain Differentiation of the Axons. Results and Probl Cell Differ. In *Cell Biology of Axon.* Ed. Koenig, N.Y. PMID: 19343313

Publication Acknowledgements:

Lee, K., Seifert, B.A., Shimelis, H., Ghosh, R., Crowley, S.B., Carter, N.J., Doonanco, K., Foreman, A.K., Ritter, D.I., Jimenez, S., Trapp, M., Offit, K., Plon, S.E., Couch, F.J. (2019) Clinical validity assessment of genes frequently tested on hereditary breast and ovarian cancer susceptibility sequencing panels. *Genet Med*. Jul; 21(7): 1497-1506. doi: 10.1038/s41436-018-0361-5. PMID: 30504931. ***Acknowledged for help with L/S and editing and suggestions on manuscript.***

Seifert, B.A., McGlaughon, J.L., Jackson, S.A., Ritter, D.I., Roberts, M.E., Schmidt, R.J., Thompson, B.A., Jimenez, S., Trapp, M., Lee, K., Plon, S.E., Offit, K., Stadler, Z.K., Zhang, L., Greenblatt, M.S.,

Ferber, M.J. (2019) Determining the clinical validity of hereditary colorectal cancer and polyposis susceptibility genes using the Clinical Genome Resource Clinical Validity Framework. *Genet Med*. Jul; 21(7): 1507-1516. doi: 10.1038/s41436-018-0373-1. PMID: 30523343. ***Acknowledged for help with L/S and editing and suggestions on manuscript.***

Grant, A.R., Cushman, B.J., Cavé, H., Dillon, M.W., Gelb, B.D., Gripp, K.W., Lee, J.A., Mason-Suares, H., Rauen, K.A., Tartaglia, M., Vincent, L.M., Zenker, M. (2018) Assessing the gene-disease association of 19 genes with the RASopathies using the ClinGen gene curation framework. *Hum Mut.* 39(11):1485-1493. doi: 10.1002/humu.23624. PMID: 30311384. ***Acknowledged for help with L/S and editing and suggestions on manuscript***

INVITED TALKS/ PRESENTATIONS

Invited Talks:

Thaxton, C. (2018). Defining disease entities. MonDO Disease Ontology Workshop, Nov 2018. Boston, MA.

Thaxton, C. (2018). Workshop on biocuration. The Open Roadmap for Open Science Tools, August 2018. Berkely, CA, USA.

Thaxton, C., McGlaughon, J., Goldstein, J. (2018). Hypothesis-assisted.is time trial: a test of an annotation tool for gene:disease biocuration. IAnnotate Symposium 2018, June 2018, San Francisco, CA, USA.

Thaxton, C., Goldstein, J., DiStefano, M., Wallace K., Witmer, D., Haendel, M., Hamosh, A., Rehm, H., Berg, J.S. (2018). Defining and refining disease nomenclature based on gene-focused curations in the age of genomic medicine. Curating the Clinical Genome 2018 platform presentation, May 2018, Hinxton, UK.

Thaxton, C., Kloth, A.K., Philpot, B.D. (2015) Identification of genetic and molecular targets for Pitt-Hopkins therapeutics. 2nd Annual Pitt-Hopkins Research Symposium. Washington, D.C. September 2015.

Thaxton, C., Philpot, B.D. (2014). Identification of genetic and molecular targets for Pitt-Hopkins therapeutics. 1st Annual Pitt-Hopkins Research Symposium. Boston, Mass. September 2014.

Thaxton, C., Bhat, M.A. (2012). Nodes of Ranvier act as barriers to restrict invasion of the flanking paranodal domains in myelinated axons. Glia in Health and Disease Meeting, Cold Spring Harbor Labs. Cold Spring Harbor, New York. July 2012. *Presented by Manzoor Bhat due to my inability to attend for personal matters.*

Bhat, M.A., Buttermore, E.D., **Thaxton, C.** (2012). Developmental Organization of the Axon Initial Segment in Cerebellar Purkinje Neurons. Myelin Gordon Conference. Barga, Italy. May 2012

Thaxton, C. (2010) The role of Neurofascins axonal domain organization in myelinated fibers. Cell and Molecular Physiology Department talks. UNC Chapel Hill, NC. March 2010.

Thaxton, C. (2007). Role of the Neurofibromatosis Type II tumor suppressor in myelination. Neuroscience Retreat. UCF Orlando, FL. October 2007.

Thaxton, C. (2007). Role of the Neurofibromatosis Type II tumor suppressor in Schwann Cell development. Miami Project to Cure Paralysis, UM Miami, FL. June 2007.

Abstract(s)/ Poster Presentation(s):

Thaxton, C., Kearns, E., Toner, K., DeCristo, D., Kurtz, C.L., Rao, S., Azzariti, D., DiStefano, M., Douglas, C., Goldstein, J., Mcglaughon, J., Ritter, D., Patel, R., Wright, M.W., Riggs, E.R., Milko, L., for the ClinGen Community Curation Working Group. (2019). ClinGen Community Curation: Crowdsourcing curation efforts from geneticists to citizen scientists. Poster presentation at The American Society of Human Genetics October 2019, Houston, TX, USA.

Milosavljevic, A., Subramanian, S., Jackson, A.R., Patel, R.Y., Paithankar, S., Iacocca, M.A., Preston, C., Wright, M.W., Costa, H., Wulf, B., Wand, H., **Thaxton, C.,** Madhavan, S., Su, A.I., Bustamante, C.D., Plon, S., for the Clinical Genome Resource Consortium. (2019). ClinGen Linked Data Hub: Scalable infrastructure for aggregation of diverse types of variant information to support pathogenicity assessment. Poster presentation at The American Society of Human Genetics October 2019, Houston, TX, USA.

Thaxton, C., McGlaughon, J., Goldstein, J., Ross, J., Mayers, M., Flowers, M., Kurtz, C.L., Berg, J.S. (2019). Annotation assisted biocuration expedites curation and enhances data capture. Poster presentation at the Curating the Clinical Genome Conference May 2019, Washington D.C., USA.

Thaxton, C., McGlaughon, J., Goldstein, J., Ross, J., Mayers, M., Flowers, M., Kurtz, C.L., Berg, J.S. (2019). Annotation assisted biocuration for variant analysis: a beta test of the utility of crowd-sourcing biocuration. Platform presentation at the IAnnotate May 2019 Meeting, Washington D.C., USA.

Wright, M. W., Dwight, S.S., Zhen, J., Thomas, C., Wulf, B., Prabhu, S., Wand, H., Azzariti, D., DiStefano, M., Goldstein, J., Harrison, S., McGlaughon, J., Riggs, E.R., Strande, N.T., **Thaxton, C.,** Babb, L., Bizon, C., Goehringer, S., Nelson, T., Zou, J., Bejerano, G., Berg, J.S., Martin, C.L., Plon, S.E., Rehm, H.L., Bustamante, C.D., for the Clinical Genome Resource (ClinGen). (2018) ClinGen's Gene Curation Interface (GCI) facilitates gold-standard consistent evaluation of the clinical relevance of genes. Poster presentation at The American Society of Human Genetics October 2018, San Diego, CA, USA.

Bostwick, B., Barry, C., Behlmann, A., Chen, C., Collins, C., Grant, A., Riggs, E., Ronza, A., Siegert, R., Sneddon, T., **Thaxton, C.,** Tokita, M., Yin, J., Zhou, X., Miller, D., Schaaf, C. for the ClinGen Intellectual Disability andAutism Gene Curation Expert Panel. (2018) Application of the ClinGen gene-disease clinical validity process to assess the strength of evidence for genes implicated in autism and intellectual disability. Poster presentation at The American Society of Human Genetics October 2018, San Diego, CA, USA.

Thaxton, C., Goldstein,J., Wallace, K., DiStefano,M., Witmer,D., Haendel,M., Hamosh, A., Rehm,., Berg, J.S. (2018) Lumping Versus Splitting: How to Approach Defining a Disease Entity for Classification in the Age of Genomic Medicine? Poster presentation at The American College of Medical Genetics and Genomics 2018, Charlotte, NC, USA.

McGlaughon, J.L., Goldstein, J.L., **Thaxton, C.**, Hemphill, S.E., Berg, J.S. (2017) The progression of the ClinGen gene clinical validity classification over time. **Two posters:** Curating the Clinical Genome June 2017, Washington D.C., USA and The American College of Medical Genetics and Genomics April 2018 Charlotte, NC, USA.

Thaxton, C., Goldstein, J., Wallace, K., DiStefano,M., Ghosh, R. Witmer, D., Riggs, E.R., Haendel, M., Hamosh, A. Rehm, H., Berg, J.S. (2017). Lumping and Splitting: An Age Old Scientific dilemma with

New Age Implications. **Two posters:** Curating the Clinical Genome June 2017, Washington D.C., USA and The American Society for Human Genetics October 2017, Orlando, FL, USA.

Ingles, J., Caleshu, C., Corty, E.W., Crowley, S.B., Dougherty, K., Goldstein, J., McGlaughon, J., Milko, L.V., Morales, A., Seifert, B.A., Semsarian, C., Strande, N., **Thaxton, C.**, Thomson, K., van Tintelen, J.P., Wallace, K., Walsh, R., Ware, J.S., Wells, Q., Whiffin, N., Wikowski, L., Hershberger, R.E., Funke,B. on behalf of the ClinGen Cardiovascular Clinical Domain WG. (2017). Use of the ClinGen Clinical Validity Framework to Evaluate the Strength of Evidence for Genes Implicated in Hypertrophic Cardiomyopathy. **Two posters and/or presentations:** Platform presentation for Curating the Clinical Genome 2017, Washington D.C., June 2017; and poster for The American Society for Human Genetics October 2017, Orlando, FL, USA,.

Thaxton, C., Pillai, A.M., Pribisko, A.L., Dupree, J.L., Bhat, M.A. (2011). Nodes of Ranvier act as barriers to restrict invasion of the flanking paranodal domains in myelinated axons. The Society for Neuroscience Annual Neuroscience Conference, Washington D.C. November 2011.

Thaxton, C., Pillai, A.M., Pribisko, A.L., Dupree, J.L., Bhat, M.A. (2010). Nodes of Ranvier act as barriers to restrict invasion of the flanking paranodal domains in myelinated axons. Cell and Molecular Physiology Research Day. UNC Chapel Hill, NC. September 2009.

Green, J.A., **Thaxton, C.**, Bhat, M.A. (2009). Identifying Whirlin's role in myelinated axons. Cell and Molecular Physiology Research Day. UNC Chapel Hill, NC. September 2009.

Thaxton, C., Pribisko, A.L., Bhat, M.A. (2009). Node for Ranvier formation and stabilization requires the axonal-specific isoform of Neurofascin (NF186). Cell and Molecular Physiology Research Day. UNC Chapel Hill, NC. September 2009.

Thaxton C., Pillai, A.M., Pribisko, A.L., Dupree, J.L., Bhat, M.A. (2009). Formation of paranodal axo-glial junctions requires immunoglobulin domains 5 and 6 of the glial-specific Neurofascin (NF155). Cell and Molecular Physiology Research Day. UNC Chapel Hill, NC. September 2009. ***Awarded.***

Pillai, A.M., **Thaxton, C.**, Pribisko, A.L., Cheng, J.G., Dupree, J.L., Bhat, M.A. (2009) Spatiotemporal ablation of myelinating glia-specific neurofascin (Nfasc(NF155)) in mice reveals gradual loss of axoglial junctions and concomitant disorganization of axonal domains. Great Lakes Glial Conference. Traverse City, MI. October 2009.

Thaxton C., Pillai, A.M., Pribisko, A.L., Dupree, J.L., Bhat, M.A. (2008). Axo-glial and nodal domain stability and maintenance requires Neurofascins. Cell and Molecular Physiology Research Day. UNC Chapel Hill, NC. October 2008.

Fernandez-Valle C, **Thaxton, C**, Bott, M, Walker, B, Lambert, S (2008). Merlin promotes process formation and extension in Schwann cells by restricting Rac activity to membrane domains with active ErbB2 and b1 integrin receptors. Children's Tumor Foundation Neurofibromatosis Conference, Bonita Springs, FL. June 2008.

Thaxton, C., Lopera, J., Bott M., Fernandez-Valle, C. (2006). Neuregulin and Laminin induce Schwannomin Phosphorylation. Annual Biomolecular Sciences Research Forum. UCF Orlando, Fl. August 2006.

Thaxton, C., Iacovelli, J., Bott, M., Lopera, J., Fernandez-Valle, C. (2004). Localization of Schwannomin, the Neurofibromatosis type 2 tumor suppressor, is dependent on paxillin interactions and

Cdc42/Rac-PAK phosphorylation. Annual Meeting of the American Society for Cell Biology. Washington D.C. December 2004.

Thaxton, C., Iacovelli, J., Bott, M., Geden, S., Fernandez-Valle, C. (2004) Schwann cell morphology is specified by Cdc42-PAK dependent serine 518 phosphorylation of Schwannomin and requires paxillin binding. Myelin Gordon Research Conference. Barga, Italy. May 2004.

PROFESSIONAL AFFLIATIONS

The Society for Neuroscience (since 2007)
The American Society for Human Genetics (since 2017)

PATENTS

United States Patent # US9,226,920. ***Methods of inducing and preventing neurofibromatosis in Schwann Cells.***

RESEARCH SUPPORT/ GRANTS

Completed Research Support:

Philpot (PI), **Thaxton** (Co-PI), Kloth (Co-PI)
Pitt Hopkins Research Foundation 01/01/2016-12/31/2016
Characterization and Generation of PTHS Model Mice for Rational Therapeutic Discovery
In support for future therapeutic development for PTHS, we will pursue two independent aims: (1) to uncover the neural impairments that are common across multiple PTHS mouse models, and (2) to develop new tools to analyze TCF4 expression in neuronal subtypes throughout development and adulthood. Previously we found that long-term changes in synaptic function related to experience are enhanced in multiple PTHS-related mouse models. We hypothesize that this deficit is related to altered function of a glutamate receptor (NMDA), and we will rigorously test this hypothesis using electrophysiology, biochemistry and pharmacological methods in multiple PTHS-related mouse models. Furthermore, we will develop a unique, novel binary "reporter-reinstatement" mouse that will not only allow for a stream-lined and genetically precise approach to drug discovery for PTHS, but also will allow us to determine the most efficacious time in which to reinstate TCF4 function to alleviate the pathophysiologies associated with PTHS. In all, the proposed project pursues incisive approaches that will provide guidance to the development of PTHS therapeutics.

Thaxton (PI), Philpot (Co-PI)
Brain Behavior Research Foundation 01/01/2014—12/31/2015
Modeling Pitt-Hopkins Syndrome, an Autism Spectrum Disorder, in transgenic mice harboring a pathogenic dominant negative mutation in TCF4
Current transgenic mouse models of *TCF4*, whether conventional or conditional, do not recapitulate the behavioral patterns present in PTHS. Furthermore, clinical data has revealed that the majority of PTHS patients have small point mutations instead of complete deletion of the TCF4 gene. Therefore, we propose to (1) develop a new mouse model of *TCF4* carrying an autosomal dominant point mutation to better mimic PTHS. Once generated, the mice will be subjected to (2) behavioral testing to determine onset of PTHS characteristics, as well as undergo (3) molecular characterization in order to uncover the function of TCF4 in the nervous system. Overall this work presents the opportunity to carry out extensive characterization of TCF4, which in turn will lead to a better understanding of PTHS and its eventual treatment.

Philpot (PI), **Thaxton** (Co-PI) 1/1/2015—12/31/2015

UPenn Center for Orphan Disease Research (CODRT)

Identification of Molecular Targets for Pitt-Hopkins Syndrome Treatments

The questionable efficacy of the available TCF4 mouse lines presents an urgent need for the generation of a mouse line modeling a PTHS associated mutation. Here, we will use three mouse models of PTHS to uncover the genes and molecular pathways regulated by TCF4. (1) The established floxed-Tcf4 mouse line ($Tcf4^{Flox}$) will allow for pan-cellular and cell-specific deletion of Tcf4. (2) Our newly generated mouse line harboring a pathogenic point mutation, human R580W (mouse R579W), the most prevalent mutation observed in PTHS ($Tcf4^{R579W}$). (3) A unique deletion model developed in our lab that lacks three of the four causative arginines located within the basic helix-loop-helix domain responsible for TCF4 function ($Tcf4^{\triangle 574\text{-}579}$). We will isolate mRNA from either whole brain or specific brain regions from each of these lines and use whole-genome analyses to identify genes commonly affected by these varying genetic models of PTHS. Comparison the genes symmetrically and asymmetrically affected by these diverse PTHS mutation mouse models will provide invaluable information into the pathophysiology of PTHS and the most rational path towards designing therapeutic strategies to treat all aspects of PTHS.

Thaxton (PI), Philpot (Co-PI), Zylka (Co-PI) 10/1/2013—9/30/2014

Pitt Hopkins Research Foundation

Identification of genetic and molecular targets for Pitt-Hopkins Therapeutics

There is a great, unmet need for the rational design of therapeutic treatment for Pitt-Hopkins Syndrome. A critical goal is to identify genes and molecular pathways regulated by TCF4 expression in the nervous sytem. To this end, our main objectives for this project are: (1) to uncover genes mediated by TCF4 expression in primary neurons, and (2) identify genes and pathways dysregulated by the over-expression of a pathogenic point mutation associated with PTHS.

Thaxton (PI)

1F32NS067943-01A1 2/1/2011—7/31/2012

Organization and Maintenance of Axonal Domains

The recent implication of Neurofascins in disease progression and pathology in demyelinating diseases, such as multiple sclerosis, has brought considerable focus towards the elucidation of their functions during axonal domain organization, axonal stability and axonal function. The main goals of this project are to: (1) Determine the role of NF86 during nodal biogenesis and development. (2) Determine the role of NF186 in the long-term maintenance and stabilization of axonal domains. (3) Determine whether loss of neurofascins in adults results in axonal degeneration.