BIOGRAPHICAL SKETCH

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NAME: Peter B. Crino M.D., Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): CRINOP

POSITION TITLE: Professor and Chairman, Neurology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Binghamton University	B.A.	05/1984	Psychology/Philosophy
Boston University	Ph.D.	05/1990	Neuroscience
Yale University School of Medicine	M.D.	05/1990	Medicine
Yale-New Haven Hospital	Internship	1990-1991	Medicine
University of Pennsylvania	Residency	1991-1994	Neurology
University of Pennsylvania-HHMI	Post-doc	1994-1997	Molecular Biology

A. Personal Statement

My lab has maintained an NIH funded translational research program studying developmental brain malformations linked to epilepsy, autism, and intellectual disabilities for the past 20 years. We have specific expertise in defining developmental disorders associated with aberrant mTOR signaling and we were the first lab to define the family of mTOR associated disorders ("mTORopathies"; see Crino, 2011) including focal cortical dysplasia (FCD), hemimegalencephaly, and gangliogliomа, as well as Pretzel syndrome (PS) in collaboration with the Clinic for Special Children in Lancaster, PA. A major focus of my lab over the past 2 decades has been tuberous sclerosis complex (TSC) in which we have worked on human brain tissue biomarkers as well as mouse and in vitro models. My lab has successfully implemented numerous experimental strategies in resected human tissues including immunohistochemistry, stereology, Western analysis, mRNA expression analysis, and DNA mutation analysis. We have successfully implemented cell culture model systems to study the effects of mTOR genes such as *Tsc1*, *Tsc2*, and *STRADA*, in *in vitro* models on cell development. We have optimized and implemented strategies in fetal mouse cortex using in utero electroporation to study the cell lineage marker, cell size, and cell signaling assays. We have published a number of gene expression studies in human MCD tissue in HME, TSC, and FCD. We have extensive experience testing pharmacological compounds such as the mTOR pathway inhibitors in cell culture and live animals. My recent collaborations have helped to describe variants in GATOR1 complex genes (*NPRL3* and *DEPDC5*) in FCD (Scerri et al., 2015; Sim et al., 2015) and three novel genes: a) *WDR73* associated with Galloway-Mowatt syndrome (Jinks et al., 2015) b) ZNF597 associated with HME (Griffin et al., 2017) c) TBCK associated with intellectual disability and epilepsy (Bhoj et al., 2015; Ortiz et al., 2017).

As a clinician-scientist, I have maintained a translational work ethic over the past 20 years by serving as a clinical neurologist and epileptologist (boarded in Neurology and Clinical Neurophysiology). I have served on two independent international task forces to establish diagnostic criteria for TSC and FCD. My career demonstrates a clear commitment to translational research into MCD such as HME and FCD.

B. Positions and Honors

1997-2005: Assistant Professor, Department of Neurology, University of Pennsylvania School of Medicine
2005-2012: Associate Professor, Department of Neurology, University of Pennsylvania School of Medicine
2006-2012: Director, University of Pennsylvania Epilepsy Center
2012-2016: Professor and Vice Chair for Research, Department of Neurology, Temple University School of Medicine

2012-2016: Deputy Director, Shriners Hospitals Pediatric Research Center
2016-pres: Professor and Chair, Department of Neurology, University of Maryland, School of Medicine.

Other Experience and Professional Memberships

1990	M.D., Yale School of Medicine, *cum laude*, *Alpha Omega Alpha*
1997-2003	National Alliance for Autism Research (NAAR): Tissue Advisory Board
1997-pres	Parents Against Childhood Epilepsy (PACE): Medical Advisory Board
1997-2003	Contributing Editor: *Epilepsy Currents*
2001-2004	Tuberous Sclerosis Alliance (TSA): Chairman, Professional Advisory Board
2001	ZHD1 MCHG-B S.E.P. Study Section
2002	ZNS1 SRB-H Study Section
2003	ZRG-1 SSS-5 Study Section
2007-pres	Tuberous Sclerosis Alliance (TSA): Member, Board of Directors
2001-2002	Merritt-Putnam Symposium Advisory Board
2004-2007	National Disease Research Interchange (NDRI): Member, Board of Directors
2008-2011	AES Scientific Program Committee
2009-2010	ILAE Task Force on Cortical Dysplasia
09/2011	Member NCI "Mechanisms of Cell Signaling in Cancer" Special Emphasis Panel (SEP),
2010-2013	AES Investigator's Workshop Committee
2012-2015	AES Anti-Epileptic Therapy (AET) Symposium Committee
07/2012	Chair, Department of Defense (DOD) - Tuberous Sclerosis Complex CDMRP Review Panel
09/2014	NINDS Molecular Neurogenetics (MNG) Study Section
2015-2021	Member, NINDS Developmental Brain Disorders (DBD) Study Section
2015	Co-Chair, Neurobiology of Disease Workshop, Society for Neuroscience
2015-2016	Program Chair, American Epilepsy Society meeting
2015-2016	President, Philadelphia Neurological Society

C. Contributions to Science

1) My lab was the first to demonstrate that the mTOR signaling pathway is aberrantly activated in a number of neurodevelopmental disorders characterized by malformations of cortical development (MCD). We have steadily moved the field forward over the past 10 years and coined the phrase "mTORopathies" to classify MCD associated with mutations in mTOR regulatory genes. Work in my laboratory expanded the spectrum of mTOR-associated disorders to include tuberous sclerosis complex (TSC), focal cortical dysplasia, hemimegalencephaly, and ganglioglioma. We were the first to define aberrant mTOR signaling in all of these disorders, and our findings have been recently corroborated by molecular genetic analysis. The identification multiple mTOR associated disorders has led to rapid progression of early phase 1 and phase 2 clinical trials with mTOR inhibitors and FDA approval for TSC. This body of work has changed and will continue to change the standards of care for human MCD associated with mTOR gene mutations. This entire clinical approach has been fostered and propelled by the data from my laboratory.

a. Baybis M, Yu J, Lee A, Golden JA, Weiner H, McKhann II G, Aronica, E, Crino PB. Activation of the mTOR cascade distinguishes cortical tubers from focal cortical dysplasia, *Ann Neurol,* 2004;56:478-487
b. Aronica E, Boer K, Baybis M, Yu J, Crino P. Co-expression of cyclin D1 and phosphorylated ribosomal S6 proteins in hemimegalencephaly. *Acta Neuropathol (Berl).* 2007; 114(3):287-93.
c. Tsai V, Parker WE, Orlova KA, Baybis M, Chi AW, Berg BD, Birnbaum JF, Estevez J, Okochi K, Sarnat HB, Flores-Sarnat L, Aronica E, Crino PB. Fetal Brain mTOR Signaling Activation in Tuberous Sclerosis Complex. *Cereb Cortex*. 2014 24(2):315-27.
d. Iffland PH 2nd, Baybis M, Barnes AE, Leventer RJ, Lockhart PJ, Crino PB. DEPDC5 and NPRL3 modulate cell size, filopodial outgrowth, and localization of mTOR in neural progenitor cells and neurons. *Neurobiol Dis.* 2018; 114:184-193.

2) Collaborative work from my laboratory has led to the identification of several novel genes and mutational mechanisms associated with MCD. The identification of these new genes has fostered investigation into the basic mechanisms of cortical development as well as accelerated clinical discovery for new therapeutics.

a. Leventer RJ, Scerri T, Marsh AP, Pope K, Gillies G, Maixner W, MacGregor D, Harvey AS, Delatycki MB, Amor DJ, Crino P, Bahlo M, Lockhart PJ. Hemispheric cortical dysplasia secondary to a mosaic somatic mutation in MTOR. *Neurology*. 2015 84(20):2029-32.
b. Sim J, Scerri T, Fanjul F, Miriam, Riseley, J, Gillies G, Pope K, van Roozendaal, H, Heng, J, Mandelstam, S, McGillivray, G, Macgregor, D, Kannan, L, Maixner, W, Harvey, S, Amor, D, Delatycki, M, Crino, PB, Bahlo, M, Lockhart, P, Leventer, R, Familial cortical dysplasia caused by mutation in the mTOR regulator NPRL3, *Ann Neurol*. 2015 79(1):132-7
c. Scerri T, Riseley JR, Gillies G, Pope K, Burgess R, Mandelstam SA, Dibbens L, Chow CW, Maixner W, Harvey AS, Jackson GD, Amor DJ, Delatycki MB, Crino PB, Berkovic SF, Scheffer IE, Bahlo M, Lockhart PJ, Leventer RJ. Familial cortical dysplasia type IIA caused by a germline mutation in DEPDC5. *Ann Clin Transl Neurol.* 2015;2(5):575-80.
d. Ortiz-González XR, Tintos-Hernández JA, Keller K, Li X, Foley AR, Bharucha-Goebel DX, Kessler SK, Yum SW, Crino PB, He M, Wallace DC, Bönnemann CG. Homozygous boricua TBCK mutation causes neurodegeneration and aberrant autophagy. *Ann Neurol.* 2018; 83(1):153-165.

3) My laboratory has an international reputation for investigation of the neurobiology of TSC. We have published numerous (>30) manuscripts describing differential expression of neurotransmitter receptors subunits ion channels, adhesion molecules, neuroinflammatory pathways, cytokines, and cell cycle proteins. We were the first to describe mTOR signaling abnormalities in the brains of patients with TSC. Our preclinical and clinical work set the stage for the ultimate FDA approval of everolimus for the treatment of TSC.

a. Crino PB**,** Aronica E, Baltuch G, Nathanson KL. Biallelic *TSC* gene inactivation in Tuberous Sclerosis Complex, *Neurology* 2010;74(21):1716-23.
b. Marcotte L, Aronica E, Baybis M, Crino PB. Cytoarchitectural alterations are widespread in cerebral cortex in tuberous sclerosis complex. *Acta Neuropathol.* 2012 May;123(5):685-93.
c. Moon UY, Park JY, Park R, Cho JY, Hughes LJ, McKenna J 3rd, Goetzl L, Cho SH, Crino PB, Gambello MJ, Kim S. Impaired Reelin-Dab1 Signaling Contributes to Neuronal Migration Deficits of Tuberous Sclerosis Complex. *Cell Rep*. 2015 Aug 11;12(6):965-78.
d. Mills JD, Iyer AM, van Scheppingen J, Bongaarts A, Anink JJ, Janssen B, Zimmer TS, Spliet WG, van Rijen PC, Jansen FE, Feucht M, Hainfellner JA, Krsek P, Zamecnik J, Kotulska K, Jozwiak S, Jansen A, Lagae L, Curatolo P, Kwiatkowski DJ, Pasterkamp RJ, Senthilkumar K, von Oerthel L, Hoekman MF, Gorter JA, Crino PB, Muhlebner A, Scicluna BP, Aronica E. Coding and small non-coding transcriptional landscape of tuberous sclerosis complex cortical tubers: implications for pathophysiology and treatment. *Sci Rep.* 2017;7(1):8089.

4) We have more than 15 years experience defining alterations in a number of cell signaling pathways in focal cortical dysplasia. We have published numerous manuscripts describing differential expression of neurotransmitter receptors subunits, ion channels, adhesion molecules, neural inflammatory pathways, cytokines, and cell cycle proteins. We were the first to describe mTOR signaling abnormalities in the brains of patients with FCD.

a. Crino PB, Duhaime A-C, Baltuch G, White R. Expression of glutamate and GABA A receptor subunit genes is distinct in dysplastic and heterotopic neurons, *Neurology* 2001;57:904-91
b. Hua Y, Crino PB. Single cell lineage analysis in human focal cortical dysplasia. *Cereb Cortex* 2003;13:693-9
c. Lamparello P, Baybis M, Pollard J, Hol E, Eisenstat D, Aronica E, Crino PB**.** Developmental lineage of cell types in cortical dysplasia with balloon cells, *Brain* 2007;130:2267-76.
d. Orlova KA, Tsai V, Baybis M, Heuer GG, Sisodiya S, Thom M, Strauss K, Aronica E, Storm P, Crino PB. Early Progenitor Cell Marker Expression Distinguishes Type II from Type I Focal Cortical Dysplasias, *J Neuropath Exp Neurol* 2010;69(8):850-863

5) My laboratory collaboratively identified the mutations in the gene *STRADA* as causative for a rare neurodevelopmental disorder known as “Pretzel syndrome” among the Mennonite community. *STRADA* encodes an mTOR regulatory protein and thus “Pretzel syndrome” falls under the classification of an

mTORopathy. Our work collaboratively defined the mutation, localized the protein in preclinical models and human brain, developed in vitro models for abnormal cell migration and cell polarity, and in vivo models to test the preclinical use of mTOR inhibitors such as rapamycin. We then ran a small clinical trial demonstrating for the first time that seizures in Pretzel syndrome could be prevented by rapamycin. In addition, we recently characterized a novel gene causing Galloway-Mowatt syndrome (*WDR73*).

a. Puffenberger E, Strauss KA, Ramsey KE, Craig DW, Stephan DA, Robinson DL, Hendrickson CL, Ramsay DA. Siu V,Heuer GG, Crino PB**,** Morton DH. Syndromic cortical dysplasia caused by a homozygous 7 kilobase deletion in LYK5, *Brain* 2007;130:1929-41.
b. Orlova KA, Parker WE, Heuer GG, Tsai V, Yoon J, Baybis M, Fenning RS, Strauss K, Crino PB**.** STRADA deficiency results in aberrant mTORC1 signaling during corticogenesis. *J Clin Invest* 2010; 120(5):1591-602.
c. Parker WE, Orlova KA, Parker WH, Birnbaum JF, Krymskaya VP, Goncharov DA, Baybis M, Helfferich J, Okochi K, Strauss KA, Crino PB. Rapamycin Prevents Seizures After Depletion of STRADA in a Rare Neurodevelopmental Disorder. *Sci Transl Med*. 2013;5(182):182ra53.
d. Jinks RN, Puffenberger EG, Baple E, Harding B, Crino PB, Fogo AB, Wenger O, Xin B, Koehler AE, McGlincy MH, Provencher MM, Smith JD, Tran L, Al Turki S, Chioza BA, Cross H, Harlalka GV, Hurles ME, Maroofian R, Heaps AD, Morton MC, Stempak L, Hildebrandt F, Sadowski CE, Zaritsky J, Campellone K, Morton DH, Wang H, Crosby A, Strauss KA. Recessive nephrocerebellar syndrome on the Galloway-Mowat syndrome spectrum is caused by homozygous protein-truncating mutations of WDR73. *Brain.* 201;138(Pt 8):2173-90.

Complete list of published work in MyBibliography
http://www.ncbi.nlm.nih.gov/pubmed?cmd=historysearch&querykey=5

D. Additional Information: Research Support and/or Scholastic Performance
List both selected ongoing and completed research projects for the past three years (Federal or non-Federally-supported). *Begin with the projects that are most relevant to the research proposed in the application.* Briefly indicate the overall goals of the projects and responsibilities of the key person identified on the Biographical Sketch. Do not include number of person months or direct costs.

NINDS R01NS099452 (9/1/16-8/20/21)
"The Role of GATOR1 in Cortical Malformations"
Principal Investigator , Crino
This grant investigates how individual components of the GATOR1 complex regulate normal cortical development.

NINDS R01NS089552-01 EUREKA (9/30/2014 – 07/31/2019)
"Discovery of Novel Molecular Abnormalities Underlying Non-Lesional Focal Epilepsy"
MPI, Winawer and Crino
The purpose of this grant is to investigate somatic gene mutations in non-lesional neocortical epilepsy and to functionally characterize new mutations in vitro.

NINDS R01NS094596-01A1 (07/01/2016 – 06/30/2021)
"Identification and Molecular Characterization of Somatic Mutations in MCD"
MPI Heinzen and Crino
Major Goals: The purpose of this grant is to define the functional effects of gene mutations identified in human brain malformations *in vitro* and *in vivo*.

Completed Research Support:

Completed in Past 3 years
NINDS R01NS082343-01 (10/1/13-4/1/17; NCE)
"Detection of Human Papilloma Virus in Cortical Dysplasia"
Principal Investigator, Crino

NINDS R41NS093970-01 (9/30/2015 – 08/31/2017)

“mTOR Substrate Phosphorylation: A New Bioassay for Therapeutics”
Principal Investigator, Crino

NINDS R21NS087181-01 (5/01/2014-4/30/2016)
“Using Patient Derived Neurons for Epilepsy Drug Discovery”
Principal Investigator, Crino

Citizens United for Research in Epilepsy (C.U.R.E.; 9/1/12-8/31/14)
Principal Investigator, Crino
A Novel Transposon Causes Focal Cortical Dysplasia