Mark Zervas, Ph.D.

http://www.linkedin.com/pub/mark-zervas/17/11b/466

Senior Scientist
Amgen, Dept. of Neuroscience

Phone: (401) 410-3554
Email: mzervas@gmail.com

OBJECTIVES

- Seeking a deeper leadership role and career growth opportunity
- Looking to lead drug discovery efforts to better treat neurological diseases

SKILLS

- Scientific Leadership
- Excellent Communication
- Project Management
- External Outreach
- Team Building
- Clinical Drug Development
- Behavioral Pharmacology
- Assay Development
- Disease Modeling
- Mouse Genetics
- Primary Neural Cultures
- Develop Research Tools
- IPSC-neuron characterization
- Prepare Data Reports
- Industry-Academic Liaison

DRUG DISCOVERY (Niemann-Pick Disease Type C (NPC)

- Developed *in vitro* assay to test mechanism of substrate deprivation using cortical neurons
- Demonstrated *in vivo* efficacy (reduced neuronal storage material and corrected neurological disease phenotypes) in murine & feline models of rare genetic disorder (NPC)
- Conducted pre-clinical studies, which advanced Zavesca (Miglustat) to clinic to treat NPC
- Findings led to approval of Zavesca to treat NPC (European Union, Canada, and South Korea)

PROFESSIONAL EXPERIENCE

AMGEN, Senior Scientist (January 2014-Current)

Current responsibilities

- Identify, present, and develop novel targets and disease mechanisms to senior leadership
- Recruit, build, and lead team to validate target biology using *in vitro* assays
- Advance mitochondrial assays (e.g. Biolog) to support Parkinson's Disease
- Develop novel cellular assays as part of a discovery effort in Neuroscience
- Induced Pluripotent Stem Cell (IPSC)-derived neuronal characterization and target validation
- Plan, initiate, and lead international multi-site collaborations (2016 and 2018)
- Experimental design, data analysis, preparation and presentation of findings

Visiting Scientist at deCODE Genetics *(February-August, 2017)*

- International team building
- Analyze human sequence data to investigate somatic mosaicism in neurological diseases
- Identify associations between genetic variants and Autism / Progressive Supranuclear Palsy

Recent responsibilities *(2014-2016)*

- Led *in vivo* behavioral pharmacology team consisting of six personnel
- Established cross training program to enhance individual and team *in vivo* skill sets
- Worked in small teams to validate and conduct novel mouse behavioral assays (PKPD)
- Responsible for behavioral assays for neuropathic pain program
- Planned, led, implemented cross site transition of *in vivo* behavioral assays

BROWN UNIVERSITY, Manning Assistant Professor of Biology (July 2006-December 2013)

Managing skills

- Established a research lab that used sophisticated mouse genetic approaches
- Directed an academic research lab with as many as ten full time members

- Managed large research budgets from 14 funded grants (see below for details)
- Published research findings in top tier journals (see below for details)
- Mentored Ph.D. students, postdoctoral fellows, undergraduates, research associates
- Designed and led graduate and advanced undergraduate courses at Brown University

Disease modeling (in vivo)

- Developed a novel mouse model that recapitulates cellular and behavioral features of a human developmental disorder, Tuberous Sclerosis (TS)
- Utilized genetic inducible fate mapping and genetic circuit tracing strategies to link *Tsc1* gene function to neural circuit formation, function, and behavior in a TS mouse model
- Established collaborations to characterize neuronal physiology and neural circuit function in TS
- Developed behavioral analyses to quantify seizures and repetitive grooming behaviors in mice
- Tested doses and delivery routes of mTOR inhibitors to ameliorate disease phenotypes
- Established novel approaches to control mosaicism in blastocysts and follow the contribution of mutant and genetically unaffected cells to distinct tissues and cell types

Mouse genetics and discovery research (in vivo)

- Developed and utilized transgenic *Wnt1-CreER* and *Wnt1-YFP* mouse lines
- Established genetic inducible fate mapping to show that *Wnt1*-expressing progenitors are the *in vivo* source of midbrain dopamine neurons
- Used RNA *in situ* hybridization, FACS, quantitative Real Time PCR (qRT-PCR) to characterize the molecular identity of dopamine neuron progenitors from developing mouse embryos
- Generated a conditional $Wnt1^{fl/fl}$ line of mice with recombineering/homologous recombination
- Showed the deletion of a molecularly and spatially distinct progenitor pool results in dopamine neuron loss in medial ventral tegmental area and pronounced behavioral deficits
- Linked WNT signaling, cell cycle dynamics, and dopamine neuron fate with birthdating *in vivo*

Embryonic stem (ES) cell experience

- Utilized five-stage programming protocol to generate dopamine neurons from mouse ES cells
- Established and led a collaboration with transgenic facility to produce novel $Wnt1^{fl/fl}$ and *Wnt1-YFP* primary embryonic stem cell lines from inner cell mass cells from blastocysts
- Used signaling molecules to test concentration dependent influences on cellular programming
- Utilized RNA analysis, qRT-PCR, and next generation sequencing to identify gene regulatory networks underpinning stem cell programming into dopamine neurons
- Showed that *Wnt1* is critical for deriving Calbindin-expressing dopamine neurons from ES cells

Unique technical skills

- Immunolabeled-thin layer chromatography to determined ganglioside accumulation in NPC
- Cell culture, confocal microscopy, and morphometric analysis of primary cortical neurons
- Expert at small and large animal surgery to harvest fresh and fixed tissue from the same brain to conduct biochemical and cellular analyses of treated versus untreated (control) animals
- Expert at mouse embryonic dissection with application to cell sorting and molecular profiling
- Established treatment paradigm based on substrate deprivation and disease endpoints for NPC
- Unbiased systematic random sampling and stereology to quantify phenotypes *in vitro* & *in vivo*
- Used Multiplex Ligation-dependent Probe Amplification to quantify mosaicism in mutant mice

EDUCATION

- Ph.D. Neuroscience, Albert Einstein College of Medicine, 1993-2000
- B.S. Chemistry, University of Massachusetts at Boston, 1989-1993

INNOVATION: FUNDED RESEARCH PROJECTS (selected from 14 awards)

- Timing of mosaic gene deletion in mouse blastocysts and multi-tissue disease development in Tuberous Sclerosis. *DOD-CDMRP Idea Development Award* (2014-2017), PI: **Zervas M**
- Linking genetic mosaicism, neural circuit abnormalities and behavior. *Simons Foundation Autism Research Initiative*. (2013-2015), PI: **Zervas M**
- Temporal loss of *Tsc1*: Neural development and brain disease in Tuberous Sclerosis. *DOD-CDMRP Idea Development Award*. (2012-2015), PI: **Zervas M**
- Determining the transcriptional regulation and cell signaling events that shape the molecular identity of dopamine neuron progenitors and specify subtypes of midbrain dopamine neurons. *NIH/NIGMS RI Hospital COBRE Center for Stem Cell Biology*. (2010-2015), PI: **Zervas M**

PRODUCTIVITY: PUBLICATIONS (selected from 29 papers)

- Walters GB, Gustafsson O, Sveinbjornsson G, Eiriksdottir VK, Agustsdottir AB, Jonsdottir GA, Steinberg S, Gunnarsson AF, Magnusson MI, Unnsteinsdottir U, Lee AL, Jonasdottir A, Sigurdsson A, Jonasdottir A, Skuladottir A, Jonsson L, Nawaz MS, Sulem P, Frigge M, Ingason A, Love A, Norddhal GL, **Zervas M**, Gudbjartsson DF, Ulfarsson MO, Saemundsen E, Stefansson H, Stefansson K. (2018). MAP1B mutations cause intellectual disability and extensive white matter deficit. *Nat Commun* 9(1):3456. doi: 10.1038/s41467-018-05595-6
- Hagan N, Guarente J, Ellisor D, **Zervas M** (2017). The temporal contribution of the *Gbx2* lineage to cerebellar neurons. *Front Neuroanat* 11:50. doi: 10.3389/fnana.2017.00050
- Brown S, **Zervas M** (2017). Temporal expression of *Wnt1* defines the competency state and terminal identity of progenitors in the developing cochlear nucleus and inferior colliculus. *Front Neuroanat* 11:67. doi: 10.3389/fnana.2017.00067
- Dingle YL, Xiong KB, Machan JT, Seymour KA, Ellisor D, Hoffman-Kim D, **Zervas M** (2016). Quantitative analysis of dopamine neuron subtypes generated from mouse embryonic stem cells. *bioRxiv* doi:http://dx.doi.org/10.1101/093419
- Sahin M, Henske EP, Manning BD, Ess KC, Bissler JJ, Klann E, Kwiatkowski DJ, Roberds SL, Silva A, St. Hillaire-Clarke C, Young LR, **Zervas M**, Mamounas LA (2016). Advances and Future Directions for Tuberous Sclerosis Complex Research: Recommendations from the 2015 Strategic Planning Conference. *Pediatr Neurol* 60:1–12
- Normand EA, Crandall SR, Thorn CA, Murphy EM, Voelcker B, Browning C, Machan JT, Moore CI, Connors BW, **Zervas M** (2013). Temporal and mosaic *Tsc1* deletion in the developing thalamus disrupts thalamocortical circuitry, neural function, and behavior. *Neuron* 78:895-909
- Yang J, Brown A, Ellisor D, Paul E, Hagan N, **Zervas M** (2013). Dynamic temporal requirement of *Wnt1* in midbrain dopamine neuron development. *Development* 140:1342-1352
- Ellisor D, Rieser C, Voelcker B, Machan JT, **Zervas M** (2012). Genetic dissection of midbrain dopamine neuron development *in vivo*. *Dev Biol* 372:249-262
- **Zervas M**, Millet S, Ahn S, Joyner AJ (2004). Cell behaviors and genetic lineages of the mesencephalon and rhombomere 1. *Neuron* 43:345-357
- **Zervas M**, Somers KL, Thrall MA, Walkley SU (2001). Critical role for glycosphingolipids in Niemann-Pick disease type C. *Current Biology* 11(16):1283-1287

SCIENTIFIC PROMINENCE: INVITED LECTURES (selected from 35 invited presentations)

- Preclinical Disease Models. *Unlocking Treatments for TSC: 2015 Strategic Plan*. National Institutes of Health, Department of Defense, and Tuberous Sclerosis Alliance (2015)
- The role of *Wnt1* in establishing dopamine neurons from embryonic stem cells. *New Avenues for Brain Repair: Programming and Reprogramming the Central Nervous System*. Harvard University (2013)
- Determining how temporal and spatial deletion of *Tsc1* and mTOR dysregulation during brain development causes neurological disease in Tuberous Sclerosis. *8th Annual Pharmacology Graduate Students' Symposium:Honorary Lecture*. Stony Brook University (2011)