BIOGRAPHICAL SKETCH

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NAME: Kesterson, Robert (Bob) Allen Jr.

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

POSITION TITLE: Professor of Genetics

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
Hendrix College, Conway, Arkansas	BA	05/1983	Chemistry
Baylor College of Medicine, Houston, Texas	PhD	10/1993	Cell Biology
The Vollum Institute for Advanced Biomedical Research, OHSU, Portland, Oregon	Postdoctoral	10/1997	Neuroendocrinology

A. PERSONAL STATEMENT

A key objective of this application is to generate and utilize novel genetic mouse models. As Director of the UAB Transgenic & Genetically Engineered Models (TGEMs), I am uniquely able to support the goals of this proposal in addressing the generation, tracking, genotyping, and phenotyping of genetically engineered animal models. I have over 25 years of direct experience working with molecular data to generate novel transgenic and gene knockout animal models of human disease, including design of DNA constructs, ES cell development and culture, microinjection of both fertilized embryos and blastocysts, and phenotypic characterization unique mouse and rat models of human disease. As a graduate student at Baylor College of Medicine, Dr. Franco DeMayo trained me in DNA microinjection procedures. These skills were expanded as a postdoctoral fellow with Roger Cone (OHSU) where I learned embryonic stem cell methodologies making several melanocortin receptor knockout models with our collaborator, Dr. Malcolm Low. As a PI at Vanderbilt, I made several transgenic and knockout mouse models prior to relocating my laboratory to UAB and also become the Director of the TGEMs in 2004. In this capacity, I meet with investigators (and his/her staff) to review all aspects of a project, including overall design of the construct (promoter, cDNA, target tissue-specificity, etc) for transgenic gain-of-function experiments, or in the case of gene targeting experiments, known targeting frequency of the gene of interest (if previously targeted), sequence analyses, probe design, and screening strategies. I also provide consultation for on line database searches of available ES cell clones generated by the various mouse mutagenesis consortiums, and personally conduct searches as needed. I have created and studied >140 knockout/knock-in mouse models (with over half of these recently made with commercially purchased ES cells). Most recently, my group has incorporated emerging nuclease-based technologies (ZFNs, TALENs, and CRISPR/Cas9) to more quickly make mouse models as well as other species including rats and fishes. Publications highlighting my qualifications for this project include:

a) O'Connor, A.K., Malarkey, E.B., Berbari, N.F., Croyle, M.J., Haycraft, C.J., Bell, P.D., Hohenstein, P., Kesterson, R.A., Yoder, B.K. An inducible CiliaGFP mouse model for in vivo visualization and analysis of cilia in live tissue. **Cilia**. 2013 Jul 3;2(1):8. PMCID: PMC3700774
b) *Kesterson, R.A., *Coste, S.C., Heldwein, K.A., Stevens, S.L., Hill, J.K., Heard, A.D., Murray, S.E., Pantely, G.A., Hohimer, A.R., Hatton, D.C., Phillips, T.J., Finn, D.A., Low, M.J., Rittenberg, M.B., Stenzel, P., Stenzel-Poore, M.P. Aberrant Appetite Control and Impaired Cardiovascular Function in Mice Lacking Corticotropin-Releasing Hormone Receptor-2 (2000) **Nature Genetics** 24:403-409 *Co-first author
c) Brooks, W.S., Kesterson, R.A., Schoeb, T.R., and Crawford, D.F. Disruption of G2E3 Causes Early Embryonic Lethality, **J Biol Chem**. 2008 Aug 8;283(32):22304-15 PMCID: PMC2494922

d) Kumar, K.G., Trevaskis, J.L., Lam, D.D., Sutton, G.M., Koza, R., Chouljenko, V.N., Kousoulas, K.G., Rogers, P.M., Kesterson, R.A., Thearle, M., Ferrante, A.W., Mynatt, R.L., Burris, T.P., Dong, J.Z., Halem, H.A., Culler, M.D., Heisler, L.K., Stephens, J.M., and Butler, A.A., Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. **Cell Metab.** 2008 Dec:8(6):468-81 PMCID: PMC2746325

B. POSITIONS AND HONORS

Positions and Employment:

1988 -1991	Research Assistant, Dept. Med./Cardiology Division Baylor College of Medicine, Houston, TX
1988 -1993	Fellow, Cell Biology, Baylor College of Medicine, Houston, TX Thesis: Regulatory Elements In Human Osteocalcin Gene Promoter Regulate Bone Specific Expression In Transgenic Mice
1991 -1993	Research Associate, Biochemistry, Ligand Pharmaceuticals, La Jolla, CA
1993 -1997	Senior Research Associate, The Vollum Inst. for Advanced Biomedical Research, Portland, OR
1997-2004	Assistant Professor, Molecular Physiology & Biophysics, Vanderbilt University Medical School, Nashville, TN Investigator, Center for Molecular Neuroscience, Diabetes Research and Training Center, Center for Nutritional Research
2004-2008	Assistant Professor, Department of Genetics, Division of Genomics Director of UAB Transgenic Animal/Embryonic Stem Cell Resource. Member, Comprehensive Cancer Center (CCC), Arthritis and Musculoskeletal Center (AMC), Clinical Nutrition Research Center (CNRC), Recessive PKD Research and Translational Core Center (RPKDCC), and Civitan International Research Center (CIRC), Center for Metabolic Bone Disease (CMBD), Diabetes Research Training Center (DRTC)
2008-2013	Associate Professor, Department of Genetics, Division of Research
2012-	Chair, UAB Institutional Animal Use & Care Committee (IACUC)
2013-	Professor, Department of Genetics, Division of Research

Other Experience and Professional Memberships

1988 -1993	Baylor College of Medicine Fellowship in Cell Biology
1991 -1993	The American Society for Bone and Mineral Research
1995 -1997	National Research Service Award NIDDK 1F32DK09414
	The Endocrine Society (1997-), American Diabetes Association (1999-), NAASO (2007-)
1997-	Ad Hoc Reviewer, Journal of Molecular Endocrinology, Endocrinology, Endocrine, J. Neuroendocrinology, J. Neuroscience, American Journal of Physiology, Diabetes
2000	US Patent #6,100,048 Cone et al. "Methods & Reagents for Discovering and Using Mammalian Melanocortin Receptor Agonists and Antagonist to Modulate Feeding Behavior in Animals"
2000	US Patent Application #60/216,979 Cone et al. "Melanocortin-3 Receptor Knockout Mouse"
2009-2012	American Diabetes Association (ADA) Research Grant Review Committee (RGRC)
2010-	New York State Stem Cell Science (NYSTEM) Review Committee; 2013 Chair, Neurobiology
2012	DoD (CDMRP) Study Section – Neurofibromatosis Research Program

Honors

1993	The American Society for Bone and Mineral Research – "Young Investigator Research Award"
2014	Association of American Medical Colleges (AAMC) Building Bridges and Spanning Boundaries Award: Innovations in Research and Research Education
2005, 2013-15	THP Overall Award

C. Contribution to Science

1. My early publications focused on bone biology and how the vitamin D receptor (VDR) regulates transcription through enhancer/repressor response elements located in target genes, as well as within it's own gene. I cloned the human VDR gene that allowed the identification of loss-of-function mutations in patients with rickets, and also created my first transgenic animals using promoter/reporter fusion constructs to characterize response elements. I continue to work with collaborators in the bone field to develop and characterize novel mouse and rat models to understand osteoblast and osteoclast interactions. Currently under review (in revision) at Disease Models Mechanisms (DMM) is a manuscript entitled "*Increased Trabecular Bone and Improved Biomechanics in an Osteocalcin Null Rat Model Created by CRISPR/Cas9 Technology*" is the first genetically modified rat model with a bone phenotype. This collaborative work with Dr. Jayleen Grams will help clarify the role of osteocalcin *in vivo*, and is an important aspect of the PhD theses of one of my graduate student trainees (Laura Lambert, first author). Key papers include:

a) Hughes, M., Malloy, P., Kieback, D., Kesterson, R.A., Pike, J.W., Feldman, D., and O'Malley, B.W. Point Mutations in the Human Vitamin D Receptor Gene Associated with Hypocalcemic Rickets (1988) **Science** 242:1702-1705
b) Kesterson, R.A., DeMayo, F., Stanley, L., Finegold, M.J., and Pike, J.W. Vitamin D Regulation of Human Osteocalcin Gene Expression in Transgenic Mice (1993) **Molecular Endocrinology** 7:462-467
c) Ashley, J.W., Shi, Z., Zhao, H., Li, X., Kesterson, R.A., and Feng, X. Genetic Ablation of CD68 Results in Mice with Increased Bone and Dysfunctional Osteoclasts, **PLoS ONE**, 2011;6(10):e25838 PMCID: PMC3185056

2. A primary goal of my research is to determine the underlying molecular mechanisms that influence complex mammalian behaviors. Using genetically modified mice as a model system, focus is primarily on hypothalamic signaling pathways that regulate feeding behavior and energy balance. Of particular interest are CNS melanocortin pathways that have emerged as key coordinators of metabolic status. Numerous collaborative studies are derived from examining the role of melanocortin signaling as upstream or downstream mediators of "feeding pathways" discovered using genetic, pharmacological, and neuroanatomical models.

a) Fan, W., Boston, B.A., Kesterson, R.A., Hruby, V.J., and Cone, R.D. Melanocortinergic Inhibition of Feeding Behavior and Disruption with an *Agouti*-mimetic (1997) **Nature** 385:165-168
b) Huszar, D., Lynch, C.A., Fairchild-Huntress, V., Dunmore, J.H., Smith, F.J., Kesterson, R.A., Boston, B.A., Fang, Q., Berkemeier, L.R., Gu, W., Cone, R.D., Campfield, L.A., Lee, F. Recapitulation of the Agouti Obesity Syndrome in Mice Lacking the Melanocortin-4 Receptor (1997) **Cell** 88:131-141
c) Kesterson, R.A., Huszar, D., Simerly, R.B., and Cone, R.D. Induction of Neuropeptide Y Gene Expression in the Dorsal Medial Hypothalamic Nucleus in Two Models of the Agouti Obesity Syndrome (1997) **Molecular Endocrinology** 11:630-637
d) Butler, A.A., Kesterson, R.A., Khong, K., Cullen, M.J., Pelleymounter, M.A., Dekoning, J., Baetscher, M., Cone, R.D. A Unique Metabolic Syndrome Causes Obesity in the Melanocortin-3 Receptor-Deficient Mouse (2000) **Endocrinology** 141:3518-21

3. A particularly fruitful collaboration with Dr. Brad Yoder led to our discovery that primary cilia located on hypothalamic neurons play a role in regulating energy balance, now an area of interest to many laboratories. We have developed and characterized numerous mouse (and rat) models with modified ciliary gene function for the study of cilia biology as well as translational studies of ciliopathies. These models have wide applicability and have been shared with many investigators worldwide (biosensors localized to cilia, conditional knockouts, reporters, etc.).

a) Davenport, J.R., Watts, A.J., Roper, V.C., Croyle, M.J., van Groen, T., Wyss, J.M., Nagy, T.R., Kesterson, R.A., and Yoder, B.K. Disruption of intraflagellar transport in adult mice leads to obesity and slow-onset cystic kidney disease. **Curr Biol.** 2007 Sep 18;17(18):1586-94. PMCID: PMC2084209
b) Berbari, N.F., Kin, N.W., Sharma, N., Michaud, E.J., Kesterson, R.A., and Yoder, B.K. Mutations in Traf3ip1 reveal defects in ciliogenesis, embryonic development, and altered cell size regulation, **Dev Biol.** 2011 Dec 1;360(1):66-76
c) Pasek, R.C., Berbari, N.F., Lewis, W.R., Kesterson, R.A., and Yoder, B.K. Mammalian Clusterin-associated protein 1 is an evolutionarily conserved intraflagellar transport complex B member, **Cilia** 2012 Nov 1;1(1):20 PMID: 23351563
d) Berbari, N.F., Pasek, R.C., Malarkey, E.B., Zaki Yazdi, S.M., McNair, A.D., Lewis, W.R., Nagy, T.R., Kesterson, R.A., and Yoder, B.K. Leptin resistance is a secondary consequence of the obesity in ciliopathy mutant mice, **PNAS** May 7;110(19):7796-801 PMCID: PMC3651481

4. Most recently, research interests have taken me into the cancer field as I've created novel mouse models with mitochondrial and nuclear genomes exchanged between inbred strains of mice (i.e. MNX mice) with differing susceptibilities to disease. Additionally, I now lead a group of investigators examining molecular mechanisms associated with neurofibromatosis type 1 (NF1) in which we have created several "humanized" mouse models harboring both missense and nonsense mutations found in patients. In each case, the newly created alleles are based on recurring variations found in NF1 patients, and will address our overall hypothesis that nonsense suppression therapy will slow or reverse tumor growth in animals that harbor a germ line Nf1 stop mutation. In addition to two manuscripts currently under review, papers include:

a) Fetterman JL, Zelickson BR, Johnson LW, Moellering DR, Westbrook DG, Pompilius M, Sammy MJ, Johnson M, Dunham-Snary KJ, Cao X, Bradley WE, Zhang J, Wei CC, Chacko B, Schurr TG, Kesterson RA, Dell'italia LJ, Darley-Usmar VM, Welch DR, Ballinger SW. Mitochondrial genetic background modulates bioenergetics and susceptibility to acute cardiac volume overload. **Biochem J.** 2013 Oct 15;455(2):157-67. doi: 10.1042/BJ20130029. PMID: 23924350

b) Feeley, K.P., Bray, A.W., Westbrook, D.G., Johnson, L.W., Kesterson, R.A., Ballinger, S.W. and Welch, D.R. Mitochondrial Genetics Regulate Breast Cancer Tumorigenicity and Metastatic Potential. **Cancer Res.** 2015; 75(20):4429-36. PMID:26471915, PMCID: PMC4610037

c) Toonen, J.A., Anastasaki, C., Smithson, L.J., Gianino, S.M., Li, K., Kesterson, R.A., and Gutmann, D.H. NF1 Germline Mutation Differentially Dictates Optic Glioma Formation and Growth in Neurofibromatosis-1. **Hum Mol Genet.** 2016; PMID:26908603

d) Li, K., Turner, A.N., Chen, M., Brosius, S.N., Schoeb, T.R., Messiaen, L.M. Bedwell, D.M., Zinn, K.R., Anastasaki, C., Gutmann, D.H., Korf, B.R., and Kesterson, R.A. Mice with missense and nonsense NF1 mutations display divergent phenotypes compared to NF1 patients. **Dis Model Mech.** 2016, in press

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/robert.kesterson.1/bibliography/47221793/public/?sort=date&direction=ascending

D. RESEARCH PROJECTS – ONGOING AND COMPLETED DURING THE LAST THREE YEARS:

Ongoing Research Support

P30 DK074038 Yoder (PI) 09/30/15 – 06/30/20
UAB Hepato/Renal Fibrocystic Diseases Core Center: Engineered Models Resource (Core B)
The Engineered Mouse Resource provides technological resources and services to support research related to pathogenesis of hepatic and renal disease by creating genetic animal models related to ciliopathies.
Role: Co-Director, Core B

P30 CA-13148 Partridge (PI) 03/01/11 – 02/28/16
UAB Comprehensive Cancer Center; Transgenic Animal Shared Facility (TASF)
The TASF provides DNA and ES cell microinjection services as well as assisted reproduction services to develop animal models of cancer and related pathologies.
Role: Director, TASF

P30 DK056336 Allison (PI) 06/01/12 - 05/31/17
UAB Center for Nutrition and Obesity Research; Animal Models Core
The goal of this resource is to assist NORC members in developing transgenic mouse models relating to disturbed energy balance, and with phenotype analyses.
Role: Co-Director, Animal Models Core

P30 AR048311 Mountz (PI) 09/01/12 – 08/31/17
UAB Rheumatic Disease Core Center: Analytical Genomics and Transgenics Core (AGTC)
The goal of this facility is to provide expert services to generate and analyze genetic/genomic data, and to develop translational animal models relating to the mission of the RDCC.
Role: Director, AGTC

P30 DK079626 Garvey (PI) 03/01/13 – 02/28/17
UAB Diabetes Research Center; Animal Physiology Core
The goal of this resource is to assist DRC members with genetically modified animal model (mice and zebrafish) development and phenotype analyses of diabetic disease processes.
Role: Co-Director, Animal Physiology Core

R01 AR47830 Feng (PI) 04/01/01 – 03/31/17
RANK Signaling in Osteoclast Differentiation and Function
The major goals of this project are to establish the role of a newly identified RANK cytoplasmic domain via structure function studies using in vitro models systems and novel animal models.
Role: Co-Investigator

R01AA012153 Kedishvili (PI) 2/01/11 – 11/30/16

Short-Chain Dehydrogenases in Retinol/Sterol Metabolism
The goal of these studies is to determine the contribution of RDH-E2 and RDH-E2S to retinoic acid biosynthesis, as well as the role of retSDR1 in the regulation of retinoic acid levels during embryogenesis and in adulthood.
Role: Co-Investigator

Completed Research Support

UAB CCC Pilot PPG Carroll (PI) 04/01/12 – 03/31/13
UAB Center for Neurofibromatosis Research: From Genomics to Therapeutics
The goals of this pilot PPG were to establish a collaborative set of research projects to examine basic mechanisms and translational platforms for neurofibromatosis research, and future NCI funding.
Role: PI, Project #1 Translational Mouse Models of NF1

Cystic Fibrosis Foundation Kesterson (PI) 07/01/13 – 06/30/15
Establishing Genetically Modified Rat Models of CFTR
The major goal of this study is to develop a rat model reminiscent of the mutant phenylalanine 508 deletion allele found in humans using CRISPR nuclease-based strategies.
Role: PI