BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Malcolm J. Low, MD, PhD	Professor of Physiology
eRA COMMONS USER NAME LOWMAL	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Rensselaer Polytechnic Institute, Troy, NY	BS	1979	Biomedical Program
Albany Medical College, Albany, NY	MD	1979	(joint BS/MD program)
Michael Reese Hospital, Chicago, IL	Intern & Resident	1979-1982	Internal Medicine
New England Medical Ctr, Boston, MA	Fellow	1982-1985	Endocrinology
Tufts University, Sackler School, Boston, MA	PhD	1987	Neuroscience

A. Positions and Employment

1985–1989 Assistant Professor, Dept. Medicine, Tufts University School of Medicine, Boston, MA
1990–1994 Assistant Scientist, Vollum Institute, Oregon Health & Science University
1991–2002 Associate Professor, CDB and BMB, School of Medicine, Oregon Health & Science Univ.
1995–2005 Scientist, Vollum Institute, Oregon Health & Science University
1997–2009 Collaborative Scientist, Div. of Neuroscience, Oregon National Primate Research Center
2002–2009 Professor, Dept. of Behavioral Neuroscience, Oregon Health & Science University
2005–2009 Senior Scientist and Associate Director, Center for the Study of Weight Regulation and Associated Disorders, Oregon Health & Science University
2006–2009 Affiliate Scientist, Vollum Institute, Oregon Health & Science University
2007–2009 Scientific Director, OHSU Transgenic Mouse Models Shared Resource
2009 – Professor, Departments of Molecular and Integrative Physiology and Medicine, Investigator, Brehm Diabetes Center, University of Michigan Medical School, Ann Arbor

Honors, Awards, and Other Professional Experience

1978 Alpha Omega Alpha Honorary Medical Society
1984–1989 NIH, NIDDK, Physician-Scientist K11 Career-Development Award
1988–1990 Pfizer Scholars Award for New Faculty
1990–1991 NIMH, Biological and Neurosciences Subcommittee 2 (BNS2) Study Section, Member
1992–1994 NIMH, Molecular Cellular & Developmental Neurobiology (MCDN) Study Section, Member
1995 NIH, NIDDK, Endocrinology Research Program Advisory Committee, Member
1997–2000 Editorial Board, *Endocrinology*
1997–Present Editorial Board, *Pituitary*
2000–2001 Scientific Advisory Board, Portland Alcohol Research Center
2001 U.S. Patent no.: 6,278,038, “Melanocortin receptors and their usefulness”
2001–2004 NIH, CSR, Endocrinology (END) Study Section, Member
2004–2005 NIH, CSR, Integrative Physiology of Obesity and Diabetes (IPOD) Study Section, Member
2004–2005 Scientific Advisory Board, Oregon National Primate Research Center
2006 U.S. Patent no.: 7,125,979, “Upstream control elements of the POMC gene and their use”
2008 U.S. Patent no.: 7,459,432 B2, “Modification of feeding behavior”

B. Selected Peer-Reviewed Publications (in chronological order, from >130 publications)

Low MJ, Goodman RH, Hammer RE, Habener JF, Palmiter RD, and Brinster RL (1985) Tissue-specific processing of pre-prosomatostatin encoded by a metallothionein-somatostatin fusion gene in transgenic mice. *Cell* **41**:211-219.

Low MJ, Lechan RM, Hammer RE, Brinster RL, Habener JF, Mandel G, and Goodman RH (1986) Gonadotroph-specific expression of metallothionein fusion genes in pituitaries of transgenic mice. *Science* **231**:1002-1004.

Hammer GD, Fairchild-Huntress V, and Low MJ (1990) Pituitary-specific and hormonally regulated gene expression directed by the rat proopiomelanocortin promoter in transgenic mice. *Mol Endocrinol* **4**:1689-97.

Liu B, Hammer GD, Rubinstein M, Mortrud M, and Low MJ (1992) Identification of DNA elements cooperatively activating POMC gene expression in the pituitary gland of transgenic mice. *Mol Cell Biol* **12**:3978-3990.

Low MJ, Liu B, Hammer GD, Rubinstein M, and Allen RG (1993) Posttranslational processing of proopiomelanocortin (POMC) in mouse pituitary melanotroph tumors induced by a POMC-Simian virus 40 large T antigen transgene. *J Biol Chem* **268**:24967-24975.

Japón MA, Rubinstein M, and Low MJ (1994) In situ hybridization analysis of anterior pituitary hormone gene expression during fetal mouse development. *J Histochem Cytochem* **42**:1117-1125.

Allen RG, Carey C, Parker JD, Mortrud MT, Mellon SH, and Low MJ (1995) Targeted ablation of pituitary POMC cells by Herpes Simplex virus-1 thymidine kinase differentially regulates messenger RNAs encoding the ACTH receptor and aldosterone synthase in the mouse adrenal gland. *Mol Endocrinol* **9**:1005-1016.

Rubinstein M, Mogil JS, Japón M, Chan EC, Allen RG, and Low MJ (1996) Absence of opioid stress-induced analgesia in mice lacking β-endorphin by site-directed mutagenesis. *Proc Natl Acad Sci USA* **93**:3995-4000.

Kelly MA, Rubinstein M, Asa S, Zhang G, Saez C, Bunzow JR, Allen R, Hnasko R, Ben-Jonathan N, Grandy DK, and Low MJ (1997) Pituitary lactotroph hyperplasia and chronic hyperprolactinemia in dopamine D2 receptor-deficient mice. *Neuron* **19**:103-113.

Rubinstein M, Phillips TJ, Bunzow JR, Falzone TL, Dziewczapolski G, Zhang G, Fang Y, Larson JL, McDougal J, Chester JA, Saez C, Pugsley TA, Gershanik O, Low MJ, and Grandy DK (1997) Mice lacking dopamine D4 receptors are supersensitive to ethanol, cocaine, and methamphetamine. *Cell* **90**: 901-911.

Chen W, Kelly MA, Opitz-Araya X, Thomas RE, Low MJ, and Cone RD (1997) Exocrine gland dysfunction in MC5-R deficient mice: evidence for coordinated regulation of exocrine gland function by melanocortin peptides. *Cell* **91**:789-798.

Kelly MA, Rubinstein M, Phillips TJ, Lessov CN, Burkhart-Kasch S, Zhang G, Saez C, Bunzow JR, Fang Y, Gerhardt G, Grandy DK, and Low MJ (1998) Locomotor activity in D2 dopamine receptor-deficient mice is determined by gene dosage, genetic background, and developmental adaptations. *J Neurosci* **18**:3470-9.

Young JI, Otero V, Cerdán, Falzone TL, Chan EC, Low MJ, and Rubinstein M (1998) Authentic cell-specific and developmentally regulated expression of proopiomelanocortin genomic fragments in hypothalamic and hindbrain neurons of transgenic mice. *J Neurosci* **18**: 6631-6640.

Phillips TJ, Brown KJ, Burkhart-Kasch S, Wenger, C, Kelly MA, Rubinstein M, Grandy DK, and Low MJ (1998) Alcohol preference is markedly reduced in mice lacking DAD2 receptors. *Nature Neurosci* **1**:610-615.

Coste SC, Kesterson RA, Heldwein KA, Stevens SL, Heard AD, Hollis JH, Murray SE, Hill JK, Pantley GA, Hohimer AR, Hatton DC, Phillips TJ, Finn DA, Low MJ, Rittenberg MB, Stenzel P, and Stenzel-Poore MP (2000) Aberrant appetite control and impaired cardiovascular function in mice lacking corticotropin-releasing hormone receptor-2. *Nature Genetics* **24**:403-409.

Mogil JS, Grisel JE, Hayward MD, Bales JR, Rubinstein M, Belknap JK, and Low MJ (2000) Disparate spinal and supraspinal antinociceptive responses in ß-endorphin-deficient mutant mice. *Neurosci*ence **101**:709-717.

Cowley MA, Smart JL, Rubinstein M, Cerdán MG, Diano S, Horvath TL, Cone RD, and Low MJ (2001) Leptin activates anorexigenic POMC neurons through a neural network in arcuate nucleus. *Nature* **411**:480-484.

Low MJ, Otero V, Ramirez JL, Kumar U, Patel YC, and Rubinstein M (2001) Somatostatin controls the sexual dimorphism of growth hormone-regulated hepatic gene expression but not of somatic growth. *J Clin Invest* **107**: 1571-80.

Batterham RL, Cowley MA, Small CJ, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, and Bloom SR (2002) PYY 3-36, a gut hormone, physiologically inhibits food intake via a novel hypothalamic mechanism. *Nature* **418**:650-654.

Heisler LK, Cowley MA, Tecott LH, Fan W, Low MJ, Smart J, Rubinstein M, Tatro J, Holstege H, Lee C, Cone RD, and Elmquist JK (2002) Fenfluramine activates central melanocortin pathways. *Science* **297**:609-611.

Hayward MD, Pintar J, and Low MJ (2002) Selective reward deficit in mice lacking ß-endorphin and enkephalin. *J Neurosci* **22**:8251-8258.

Schuff KG, Hentges ST, Kelly MA, Binart N, Kelly PA, Iuvone PM, Asa SL and Low MJ (2002) Lack of prolactin receptor signaling in mice results in lactotroph proliferation and prolactinomas by dopamine-dependent and independent mechanisms. *J Clin Invest* **110**:973-981.

Gelman D, Noaín D, Avale ME, Otero V, Low MJ, and Rubinstein M (2003) Transgenic mice engineered to target Cre/loxP-mediated DNA recombination into catecholaminergic neurons. *Genesis* **36**:196-202.

Appleyard SM, Hayward MD, Young JI, Butler AA, Cone RD, Rubinstein M, and Low MJ (2003) A role for the endogenous opioid ß-endorphin in energy homeostasis. *Endocrinology* **144**: 1753-60.

Hentges SA, Nishiyama M, Overstreet LS, Stenzel-Poore M, Williams JT, and Low MJ (2004) GABA release from proopiomelanocortin neurons. *J Neurosci* **24**:1578-1583.

Overstreet LS, Hentges ST, Bumaschny VF, de Souza FSJ, Smart JL, Santangelo AM, Low MJ, Westbrook GL, and Rubinstein M (2004) A transgenic marker for newly born granule cells in dentate gyrus. *J Neurosci* **24**:3251-3259.

Hayward MD, Hansen ST, Pintar J, and Low MJ (2004) Operant self-administration of ethanol in C57BL/6 mice lacking ß-endorphin and enkephalin. *Pharmacol Biochem Behav* **79**:171-181.

de Souza FSJ, Santangelo AM, Bumaschny V, Avale ME, Smart JL, Low MJ, and Rubinstein M (2005) Identification of neuronal enhancers of the proopiomelanocortin gene by transgenic mouse analysis and phylogenetic footprinting. *Mol Cell Biol* **25**:3076-3086.

Appleyard SM, Bailey TW, Doyle MW, Jin Y-H, Smart JL, Low MJ, and Andresen MC (2005) Proopiomelanocortin neurons in nucleus tractus solitarius are activated by visceral afferents and modulated by cholecystokinin and opioids. *J Neurosci* **25**:3578-3585.

Christina C, Diaz-Torga G, Baldi A, Góngora A, Rubinstein M, Low MJ, and Becú-Villalobos D (2005) Increased pituitary vascular endothelial growth factor in dopaminergic D2 receptor knockout female mice. *Endocrinology* **146**:2952-2962.

Slominski A, Pisarchik A, Plonka P, Smart JL, Tolle V, Wortsman J, and Low MJ (2005) Preservation of eumelanin hair pigmentation in proopiomelanocortin-deficient mice on a non-agouti (*a/a*) genetic background. *Endocrinology* **146**:1245-1253.

Elmer GI, Pieper JO, Levy J, Rubinstein M, Low MJ, Grandy DK, and Wise RA (2005) Brain stimulation and morphine reward deficits in dopamine D2 receptor-deficient mice. *Psychopharmacology (Berl)* **182**:33-44.

Hayward MD, and Low MJ (2005) Naloxone's suppression of spontaneous and food conditioned locomotor activity is diminished in mice lacking either the dopamine D2 receptor or enkephalin. *Brain Res Mol Brain Res* **140**:91-98.

de Souza FSJ, Bumaschny VF, Low MJ, and Rubinstein M (2005) Subfunctionalization of expression and peptide domains following the ancient duplication of the proopiomelanocortin gene in teleost fishes. *Mol Biol Evol* **22**:2417-2427.

Hentges ST, Low MJ, and Williams JT (2005) Differential regulation of synaptic inputs by constitutively released endocannabinoids and exogenous cannabinoids in hypothalamus. *J Neurosci* **25**:9746-9751.

Kumar TR, Schuff KG, Nusser KD, and Low MJ (2006) Gonadotroph-specific expression of the human follicle stimulating hormone ß gene in transgenic mice. *Mol Cell Endocrinol* **247**:103-115.

Smart JL, Tolle V, and Low MJ (2006) Glucocorticoids exacerbate obesity and insulin resistance in neuronal-specific proopiomelanocortin deficient mice. *J Clin Invest* **116**:495-505.

Risbrough V, Masten V, Caldwell S, Paulus M, Low MJ, and Geyer MA (2006) Differential contributions of dopamine D1, D2, and D3 receptors to MDMA-induced effects on exploratory locomotor behavior patterns in mice. *Neuropsychopharmacology* **31**:2349-2358.

Job MO, Ramachandra V, Anders S, Low MJ, & Gonzales RA (2006) Reduced basal and ethanol stimulation of striatal extracellular dopamine concentrations in dopamine D2 receptor knockout mice. *Synapse* **60**:158-164.

Hayward MD, Schaich-Borg A, Pintar JE, and Low MJ (2006) Differential involvement of endogenous opioids in sucrose consumption and food reinforcement. *Pharmacol Biochem Behav* **85**:601-611.

Hayward MD, and Low MJ (2007) The contribution of endogenous opioids to food reward is dependent on sex and background strain. *Neuroscience* **144**:17-25.

Smart JL, Tolle V, Otero-Corchon V, and Low MJ (2007) Central dysregulation of the hypothalamic-pituitary-adrenal axis in neuron-specific proopiomelanocortin-deficient mice. *Endocrinology* **148**:647-659.

Bumaschny VF, de Souza FSJ, López Leal RA, Santagelo AM, Baestcher M, Levi DH, Low MJ, and Rubinstein M (2007) Transcriptional regulation of pituitary POMC is conserved at the vertebrate extremes in spite of great promoter sequence divergence. *Mol Endocrinol* **21**:2738-2749.

Santangelo AM, de Souza FSJ, Franchini LF, Bumaschny VF, Low MJ, and Rubinstein M. (2007) Ancient exaptation of a CORE-SINE retroposon into a highly conserved mammalian neuronal enhancer of the proopiomelanocortin gene. *PLoS Genet* **3(10)**:e166, pp. 1-14.

Appleyard SM, Marks D, Kobayashi K, Okano H, Low MJ, and Andresen MC (2007) Visceral afferents directly activate catecholamine neurons in the solitary tract nucleus. *J Neurosci* **27**:13292-13302.

Tolle V and Low MJ (2008) In vivo evidence for inverse agonism of agouti related peptide in the central nervous system of proopiomelanocortin deficient mice. *Diabetes* **57**:86-94.

Kelly MA, Low MJ*, Rubinstein M, and Phillips TJ* (2008) Role of dopamine D1-like receptors in methamphetamine locomotor responses of DRD2 knockout mice. *Genes Brain Behav* **7**:568-577. (*equal contributors)

Arttamangkul S, Quillinan N, Low MJ, von Zastrow M, Pintar J, and Williams JT (2008) Differential activation and trafficking of mu-opioid receptors in brain slices. *Mol Pharmacol* 74:972-979.

Gong L, Yao F, Hockman K, Heng HH, Morton GJ, Takeda K, Akira S, Low MJ, Rubinstein M, and MacKenzie RG (2008) Stat3 is required in hypothalamic AgRP/NPY neurons for normal energy homeostasis. *Endocrinology* **149**:3346-3354.

Hauge-Evans AC, King AJ, Carmignac D, Robinson ICAF, Low MJ, Christie MR, Persaud SJ, and Jones PM (2009) Somatostatin secreted by islet delta-cells fulfills multiple roles as a paracrine regulator of islet function. *Diabetes* **58**:403-411.

Hentges ST, Otero-Corchon V, Pennock RL, King CM, and Low MJ (2009) Proopiomelanocortin expression in both GABA and glutamate neurons. *J Neurosci* (in press)

C. Research Support

Ongoing Research Support

NIH, 1 R01 DK068400-05 (Low) 08/01/04-06/30/10
Proopiomelanocortin gene expression and obesity. The overall goal of this project is to elucidate the transcriptional machinery responsible for POMC gene expression in the brain and to develop novel molecular tools for the further physiological characterization of POMC peptides and co-transmitters produced in POMC neurons in the control of appetite and feeding. Role: P.I.

NIH, 2 R01 DK066604-05A1 (Low) 09/10/09-08/31/14
Neurochemistry/physiology of proopiomelanocortin neurons. The overall goal of this project is to further delineate neurochemically distinct subpopulations of POMC neurons within the arcuate nucleus and nucleus tractus solitarius (NTS) and to match these subpopulations with their specific physiological actions in the regulation of metabolic rate and food intake. A variety of transgenic, gene knockout, and aggregation chimera models are used to investigate the function of individual POMC peptides and subgroups of arcuate POMC neurons, including those that use GABA as a co-transmitter, in the regulation of energy balance. Role: P.I.

Completed Research Support (past three years)

Collins Medical Trust (Low) 02/01/08-01/31/09
The role of proopiomelanocortin neurons in feeding and obesity: an anatomical and behavioral analysis. Subset of the aims from the R01 grant DK066604 named above prior to funding of the competitive renewal by the NIH. Role: P.I.

The Endocrine Society Bridge Funds Award (Low) 02/01/08-07/01/08
Neurochemistry/physiology of proopiomelanocortin neurons. Subset of the aims from the R56 grant DK066604 named above until funding of the R56 by the NIH. Role: P.I.

NIH, 5P60 AA010760-12 (Crabbe) 01/01/07-12/31/07
Behavioral genomics of alcohol neuroadaptation. [Portland Alcohol Research Center]
Pilot Project: Ethanol consumption and ethanol-induced behavioral sensitization in neural-specific POMC-deficient mice. (Low) The major goal of this pilot project was to test the hypothesis that central melanocortin neuropeptides modulate ethanol intake, preference, and locomotor sensitization. Role: Project Director

NIH, 1R01 MH067497-05 (Grandy) 01/01/03-07/31/07
D4 receptor-mediated effects of methylphenidate in mice. The major goal of this project was to test the hypothesis that dopamine D4 receptor function plays an important role in the pathogenesis of ADHD. Role: Co-Investigator, design and construction of additional mutant mouse models.

NIH, Fogarty International Center, 2R03 TW01233 (Low) 03/01/03-02/28/07
Neural-specific regulation of POMC gene expression. The major goals of this project were to utilize phylogenetic footprinting, in vitro transfection, and in vivo transgenic experiments to comparatively study gene expression of POMC from teleost fish and mammals in pituitary and brain. This was an international cooperative grant between the USA & Argentina in support of the aims in its parent grant DK068400. Role: P.I.