

MMPC MICROmouse Program (2009-2013)



Maren Laughlin
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Leaders

- ▶ Kate Ellacott
- ▶ Gary Cline
- ▶ Colleen Croninger
- ▶ Rick McIndoe

Eligible Project Directors/Principal Investigators:

Applicants must hold a doctoral level position but young investigators and post-doctoral fellows are encouraged to apply.

For hypothesis driven biological research, multiple project directors/principal investigators, one of whom must be an MMPC investigator. The application may originate from either the MMPC or the collaborating institution.

Mechanics

\$75K direct costs, 1 year. PI can request 2nd year.

Applications reviewed 4x/year (3 expert reviewers, scores and comments)

-managed by Kate, Gary and Colleen

Applications chosen for award by simple majority of MMPC steering committee

-managed by Rick

Awards made from the CBU, typically via subcontract. F&A costs negotiated.

-overseen by Rick

Progress report submitted at termination of award period

Pilot and feasibility of new phenotyping tests

Develop or miniaturize technologies

Applications of existing technologies for use in mice;

Provide new tests to phenotype mouse models of metabolic disease

Establish new types of mathematical models, informatics, databases or products that augment the mission of the center.

Examples of research-driven projects in collaboration with an MMPC

The pursuit of novel biological questions;

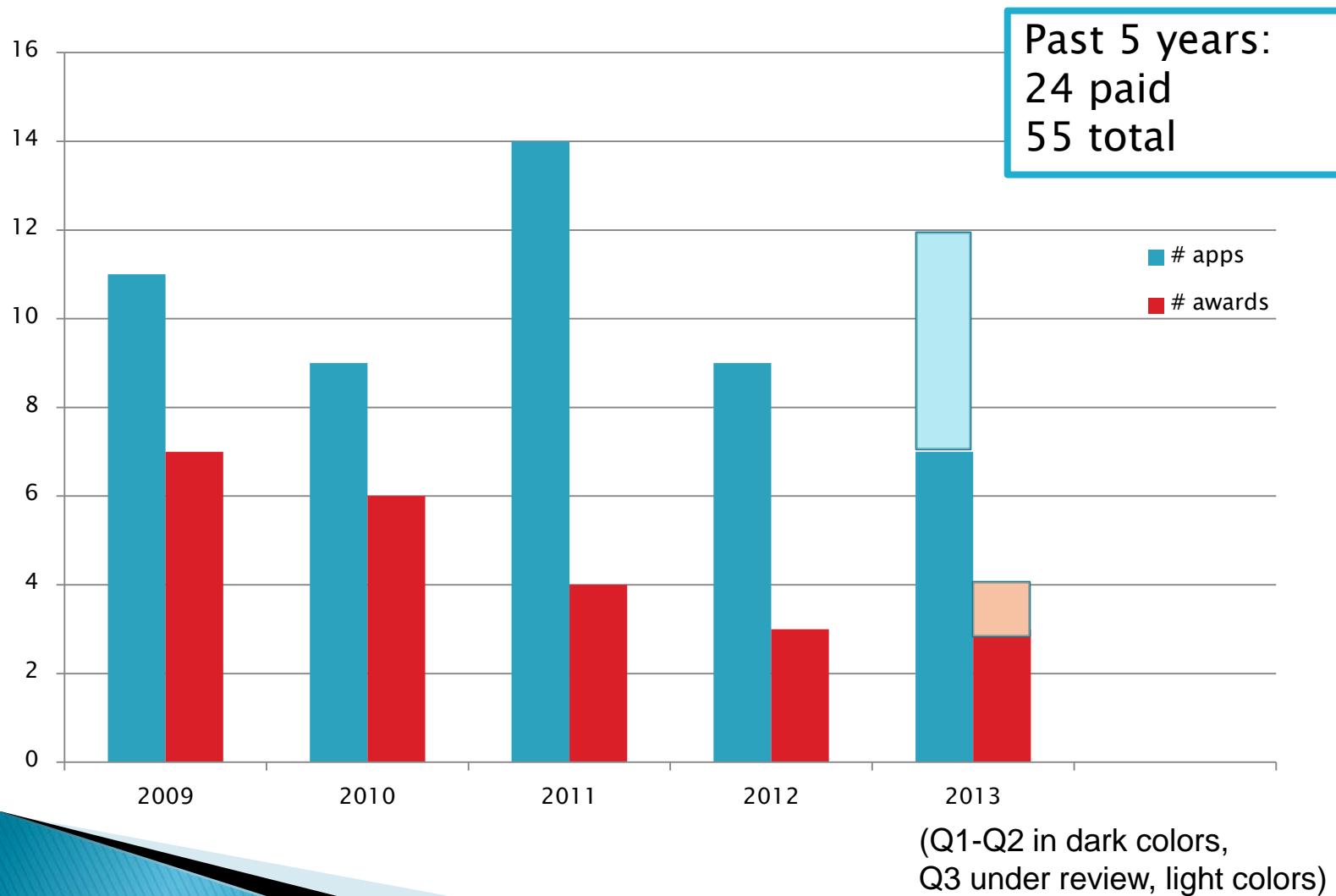
Thorough phenotyping of new models that may be important for the study of a variety of diseases or for understanding tests;

--bariatric surgery, dm complications, multiparous pregnancy, circadian rhythms, diets, energy balance, drive for physical activity

To bring together investigators with complimentary mouse models that would not normally interact;

Investigation of new molecular targets uncovered by prior MMPC studies.

MICROmouse Applications



Where are 2009-2013 MICR0mouse applications from?

Albert Einstein College of Medicine	1
Baylor College of Medicine	1
Columbia University	1
Mount Sinai School of Medicine	1
Pennington Biomedical Research Center	1
University of Arizona	1
University of California-San Francisco - School of Pharmacy	1
University of Texas Southwestern	1
Washington State University	1
University of Nebraska at Omaha	3
Wayne State University	3
Yale University	3
University of California - Davis	4
University of Cincinnati	4
University of Virginia Health System	4
University of Washington	7
Vanderbilt University	20

Investigators 2009-2013

37 Unique PI Applicants for 56 Applications

1 PI : 4 applications

5 PIs : 3 applications

6 PIs : 2 applications

25 PIs : 1 application

20 Unique PIs with Awards

4 PIs: 2 awards

16 PIs: 1 award

How to judge success?

- ★ Papers
- ★ Grants, other funding
- ★ Tests or new practices incorporated into an MMPC
- ★ Translation
- ★ Commercial products

Publications

Of completed projects,

the vast majority reported at least some progress at the completion of the award

2009: 5 of 7 produced papers

2010: 4 of 6 produced papers

2011: 2 of 4 produced papers

2012: all 3 awards to productive ongoing studies

2009 awards papers

Warangkana Pichaiwong, Kelly L. Hudkins, Tomasz Wietecha, Tri Q. Nguyen, Chiraporn Tachaudomdach, Wei Li, Bardia Askari*, Takahisa Kobayashi, Kevin D. O'Brien, Jeffrey W. Pippin, Stuart J. Shankland, Charles E. Alpers. Reversibility of Structural and Functional Damage in a Model of Advanced Diabetic Nephropathy. *JASN* June 28, 2013 vol. 24 no. 7 1088-1102

Corbin KL, Hall TE, Haile R, Nunemaker CS. A novel fluorescence imaging approach for comparative measurements of pancreatic islet function in vitro. *Islets*. 2011 Jan-Feb;3(1):14-20.

Heon Park,¹ Karen Staehling,^{2,7} Mark Tsang,¹ Mark W. Appleby,^{2,6} Mary E. Brunkow,^{2,8} Daciana Margineantu,³ David M. Hockenberry,³ Tania Habib,¹ H. Denny Liggitt,¹ George Carlson,⁴ and Brian M. Iritani^{1,#. Disruption of *Fnip1* reveals a metabolic checkpoint controlling B lymphocyte development. *Immunity*. 2012 May 25; 36(5): 769–781.}

Shi, S., A. Hida, O.P. McGuinness, D.H. Wasserman, S. Yamazaki, C.H. Johnson. Circadian Clock Gene Bmal1 Is Not Essential; Functional Replacement with its Paralog, Bmal2. *Current Biology* 20: 316-321.

Rebholz SL, Jones T, Burke KT, Jaeschke A, Tso P, D'Alessio DA, Woollett LA. Multiparity leads to obesity and inflammation in mothers and obesity in male offspring. *Am J Physiol Endocrinol Metab*. 2012 Feb 15;302(4):E449-57. *J Clin Endocrinol Metab*. 2012 Jun;97(6):E1023-31. doi: 10.1210/jc.2011-3432. Epub 2012 Apr 6.

2010 Award Papers

Plaisance EP, Henagan TM, Echlin H, Boudreau A, Hill KL, Lenard NR, Hasek BE, Orentreich N, Gettys TW. Role of beta-adrenergic receptors in the hyperphagic and hypermetabolic responses to dietary methionine restriction. *Am J Physiol Regul Integr Comp Physiol.* 2010 Sep;299(3):R740-50.

Melanocortin-4 receptor signaling is required for weight loss after gastric bypass surgery.

Hatoum IJ, Stylopoulos N, Vanhoose AM, Boyd KL, Yin DP, Ellacott KL, Ma LL, Blaszczyk K, Keogh JM, Cone RD, Farooqi IS, Kaplan LM.

Head WS, Orseth ML, Nunemaker CS, Satin LS, Piston DW, Benninger RK. Connexin-36 gap junctions regulate in vivo first- and second-phase insulin secretion dynamics and glucose tolerance in the conscious mouse. *Diabetes.* 2012 Jul;61(7):1700-7

Berkowitz, B.A., Bissig, D., Patel, P., Bhatia, A., Roberts, R., Acute systemic 11-cis-retinal intervention ameliorates abnormal outer retinal ion channel closure in diabetic mice, *Mol. Vis.* 18:372–376, 2012

2011 Award Papers

Pendergast JS, Niswender KD, Yamazaki S. Tissue-specific function of Period3 in circadian rhythmicity. *PLoS One*. 2012;7(1):e30254

Yin DP, Gao Q, Ma LL, Yan W, Williams PE, McGuinness OP, Wasserman DH, Abumrad NN. Assessment of different bariatric surgeries in the treatment of obesity and insulin resistance in mice. *Ann Surg*. 2011 Jul;254(1):73-82

What do we fund, what do we not fund?

Topic	Awarded	Not Awarded	Under Review
Diabetic Complications	6	5	1
Islet Biology	4	3	
Bariatric Surgery	4	2	
Phenomena Impacting MMPC	4	1	
Other Test Development	4	2	2
Metabolism & Nutrition	2	6	1
Total	24	19	4

Topics (for discussion)

Phenomena affecting MMPC tests—ongoing, productive

Circadian Control of Glucose Metabolism and Insulin Action	2009	Johnson, Carl
Increased risk for diabetes and obesity in offspring of multiparous mice.	2009	Woollett, Laura
Interplay between circadian disorganization and obesity	2011	Yamazaki, Shin
Risk of multi-generational programming in offspring of multiparous mice	2012	Woollett, Laura

New technology/tests—are we investing appropriately?

Metabolic Fluxes During Hyperinsulinemic Euglycemia in Insulin Resistant Mice	2010	Sunny, Nishanth
In vivo assessment of mouse muscle oxidative capacity by 31P-MRS	2011	Befroy, Douglas
Peritoneal microdialysis as an alternative to blood sampling in mice	2011	Marini, Juan
Mass spectrometry-based approach for flux analysis of in vivo liver metabolism	2013	Young, Jamey

Topics, contd. (for discussion)

Bariatric Surgery—emerging and coming together

Impact of Bariatric Surgery on Adipose Tissue Inflammation	2010	Hasty, Alyssa
Role of Melanocortin Signaling in Gastric Bypass-induced Feeding Behavior	2010	Vanhoose, Amanda
Role of Complete & Partial Gastric Bypass in Determining the Efficacy of Bariatric Surgery in the Mouse	2011	Yin, Dengping
Role of TGR5 in the metabolic benefits observed after sleeve gastrectomy surgery	2013	Cummings, Bethany

Islet Biology—should MMPC have bigger emphasis?

Nucleomic Analysis of Cell-type Specific Gene Expression in Diabetic Mouse Models	2009	Lynch, Ronald
Effects of acute deletion of selective transcription factors on mouse islets	2009	Nunemaker, Craig
β-cell gap-junctional coupling effects on plasma insulin oscillations	2010	Piston, David
Reducing glycolysis to restore optimal pulsatility in the db/db mouse	2012	Nunemaker, Craig

Topics, contd. (for discussion)

Diabetic Complications—future needs?

Long Chain Fatty Acids and Mineralocorticoid Receptor Upregulation in a Mouse Model of Diabetic Nephropathy	2009	Askari, Bardia
	2010	Berkowitz, Bruce
MRI Phenotyping of Murine Diabetic Retinopathy	2012	Berkowitz, Bruce
Phenotyping Visual Cycle Dysfunction in Diabetic Retinopathy		
A novel AMPK-interacting protein in cardiac metabolism and function	2009	Iritani, Brian
	2009	
Characterization of A New Murine Model of Cardiomyopathy in Type 2 Diabetes		O'Brien, Kevin



Grants

PI	MICROmouse	Additional Funding
Alpers, Charles	Characterization of a New Murine Model of Reversal of Diabetic Nephropathy	1R01DK083391-01A2 Podocyte depletion/ regeneration in evolution & reversal of diabetic nephropathy
Daneshgari, Firouz	Assessment of Bladder Sensory Threshold in Diabetic Mice	1R03HD061825-01 Mechanisms of Neurogenic Bladder Dysfunction in EAE Mice
Gettys, Thomas W	REMODELING OF HEPATIC LIPID METABOLISM BY DIETARY METHIONINE RESTRICTION	1R01DK096311-01 MECHANISMS OF METABOLIC REGULATION BY DIETARY METHIONINE RESTRICTION
Hasty, Alyssa	Impact of Bariatric Surgery on Adipose Tissue Inflammation	ADA Grant 1R21DK095456-01 Adipose Tissue Macrophage Iron Metabolism in Obesity

Grants

PI	MICROmouse	Additional Funding
Johnson, Carl	Circadian Control of Glucose Metabolism and Insulin Action	1R21HL102492-01 Analysis of Mammalian Circadian Mechanism with Cell-permeant Clock Proteins1
Maggio-Price, Lillian	Effect of Murine norovirus on the phenotype of LDL Receptor-Deficient mice	1R01RR032288-01 MNV-4, an Emerging Pathogen in Murine Models of Inflammatory Bowel Disease 1R21RR032289-01 Effects of Murine norovirus infection on Mouse Models of Atherosclerosis
Nunemaker, Craig	Effects of acute deletion of selective transcription factors on mouse islets	1R01DK089182-01A1, Low grade inflammation, cytokines and islet dysfunction in T2D
O'Brien, Kevin	Characterization of A New Murine Model of Cardiomyopathy in Type 2 Diabetes	John L. Locke (Foundation?)

How are we doing?

- ▶ Should we target the 2013 funding programs?
- ▶ Do we need to advertise?
- ▶ Should the competition be restructured?
- ▶ Do we need to alter requirements for investigators?