UCDAVIS MMPC Mouse Metabolic Phenotyping Center

established 2011

MMPC at UC Davis Annual Report (Y04)

NIH U24 DK092993

NIH National Institutes of Health

NIH National Institute of Diabetes and Digestive and Kidney Diseases

MMPC Steering Committee Annual Meeting
NIH, Bethsda, MD

MOUSE BIOLOGY PROGRAM

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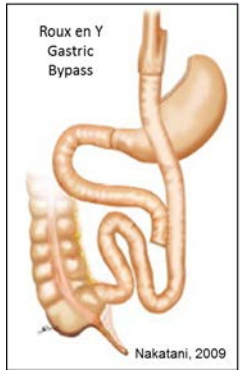
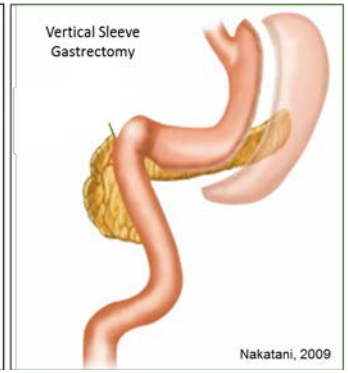
Highlights!

Bariatric Models
Brain Imaging
Continuous glucose monitoring (CGM)
iv Glucose Tolerance Test (GTT)
Telemetry
Gut Microbiome
Gnotobiotic Mouse Research Center
Gut Permeability
Energy Expenditure
Metabolomics
Ultrasonographic imaging
Website
Metrics

Bariatric Surgery Models (Core B, Animal Care)

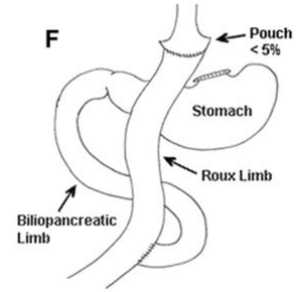




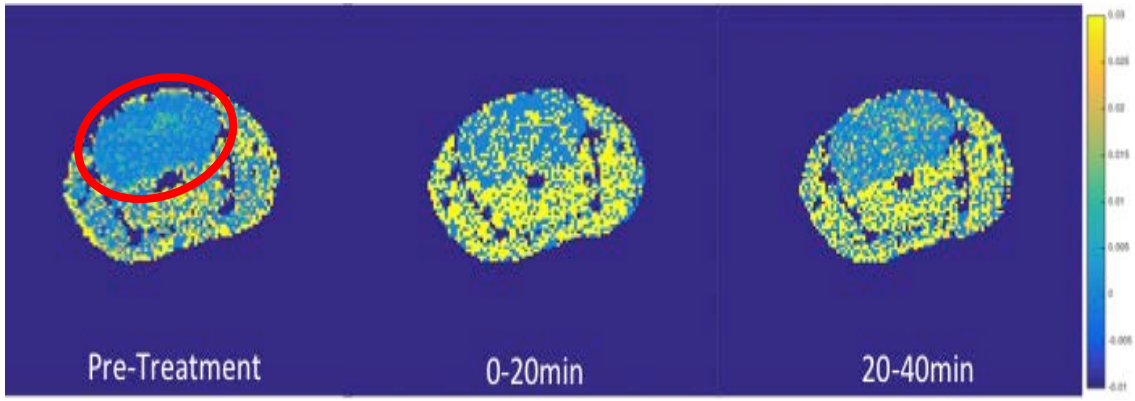
	VSG		RYGB	
	Sham	Surgery	Sham	Surgery
Number of survival surgeries	64	127	51	83
Number (%) survived at one month post-op	52 (81%)	103 (81%)	48 (94%)	56 (68%)

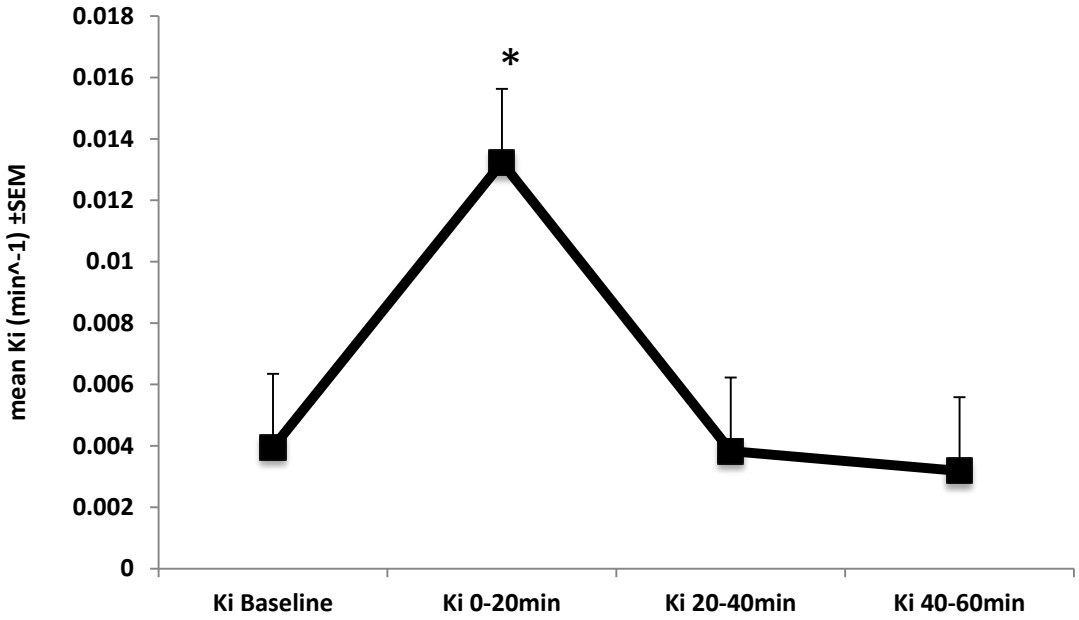
Models Development Update:

- VSG Validation study underway, UC Davis portion completed
  - males and females
  - microbiome, energy expenditure (CLAMS), fecal digestible energy, DEXA, ivGTT (VSG versus pair fed and ad lib sham controls)
- VSG models offered as service and for distribution
  - 4 requests underway
- RYGB models offered as service and for distribution
  - Refining procedure (modification of Hao *et al*, 2013)
- Cores C&D participating in service (functional analysis)
- Ileal transposition coming next



Blood Brain Barrier Permeability by MRI *(Core E, Cardio/Pathology)*





Procedure Update:

- T1 weighted MRI data is collected with 7T Bruker Biospec MRS/MRI system using Magnevist (gadolinium based) contrast agent
- Assay could be applied to kidney or tumor biology (with some modifications to protocol)

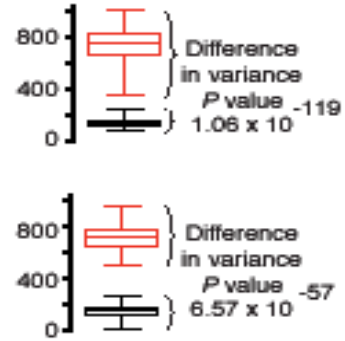
Continuous Glucose Monitoring-CGM (Core C, Endocrinology & Metabolism)

van der Meulen, T., et al., Nat Med, 2015. 21(7): p. 769-76

Gl… measurements every 5 min in diabetic ob/ob (red)
an…)

a

b



Procedure Update:

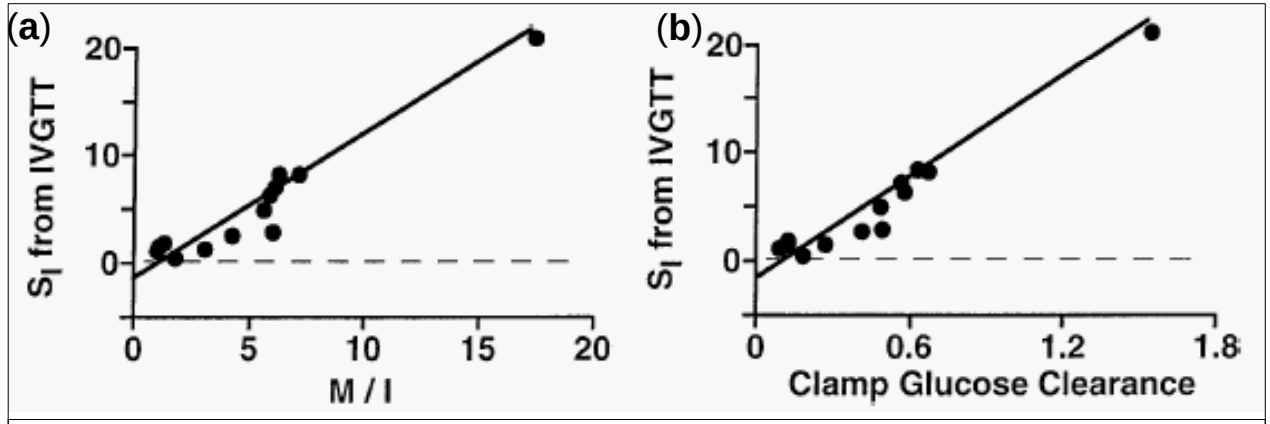
… (Core B)

…entrations in

- To be offered as a service

Intravenous Glucose Tolerance Test-ivGTT (Core C, Endocrinol & Metabol)

(Ahren and Pacini, Am. J. Physiol., 1998, 1999, 2001, 2002



Validation with insulin sensitivity and glucose clearance assessed with Clamps

Insulin sensitivity index (S_I) as measured by (**a**) IVGTT is well-correlated (r = 0.97; p< 0.0001) with insulin sensitivity and glucose clearance rates measured by (**b**) hyperinsulinemic, euglycemic clamps. M/I, glucose infusion rate during the 2nd h / mean insulin level at 60-120 min.

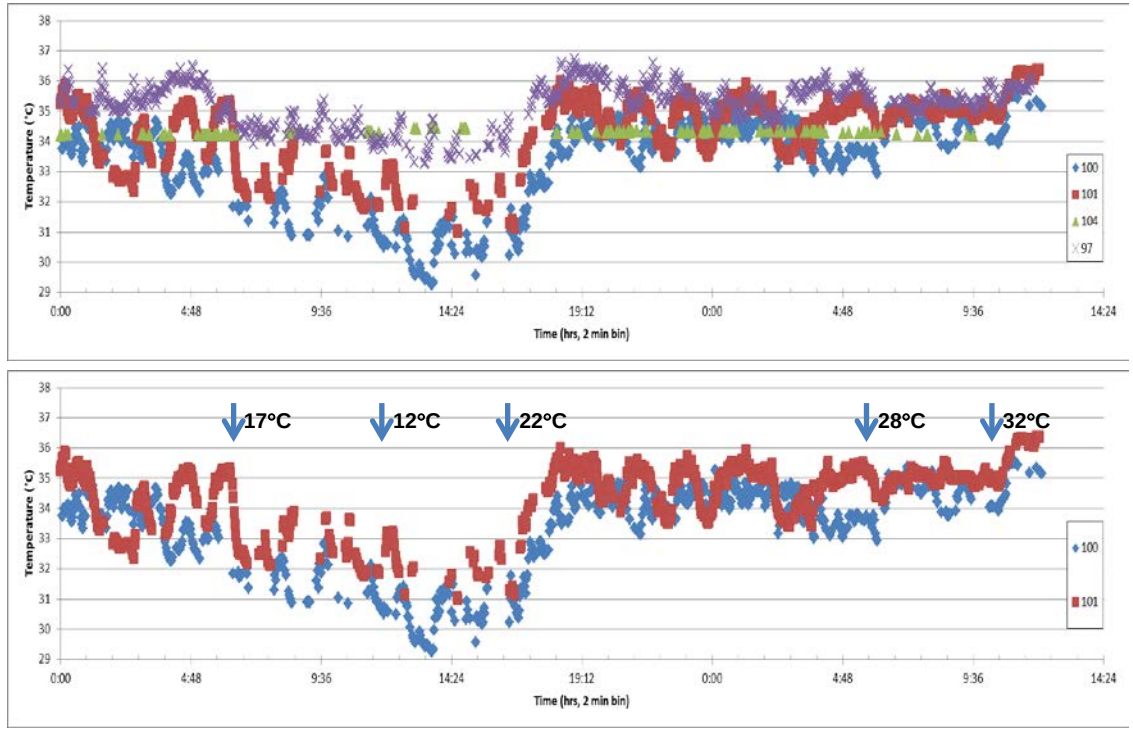
Assay Update:

- Requires 7 small (40µl) blood samples over 50 minutes following glucose IV (Core B).
- Faster & higher throughout than clamps - can also assess insulin secretion, insulin mediated + insulin independent glucose disposal (DI).
- Analysis simple math formula (computer modeling not needed; Am. J. Physiol., 2009).
- Offered as service (Core C&B) (e.g., insulin sensitivity in bariatric surgery mice)

Murine Telemetry System (Core E, Cardiovascular & Pathology)

Data Scientific Intl. Telemetry System

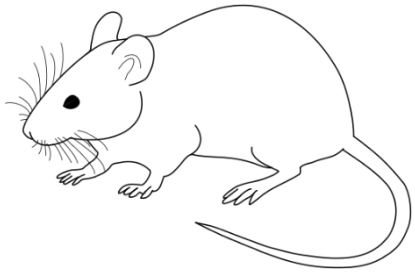
- HD-X11 or TA-F10 implantable telemeter
- Pressures: arterial, venous, left ventricular, ocular, bladder
- Biopotentials:ECG, EMG, EEG, EOG
- Temperature
- Activity (relative)
- Option of temperature controlled, or in CAMS



Assay Update:

- First (pilot) study completed (with Core D: temp ramp with RynR mutant)
- Currently accommodates 4 mice/run (upgradable to 8-16)
- Fully installed, offered as service (Core D&B)

Host-Microbiome Analysis (Core D, Body Composition)



Host

Host function

Gut
- Permeability (Ussing chambers)
- GI tract transcriptomics

Systemic

Plasma or tissue metabolomics
- Bacterially derived metabolites

Microbiome/Microbiota

Archaea, Bacteria, Fungi, Viruses

Phylogenetic Classification

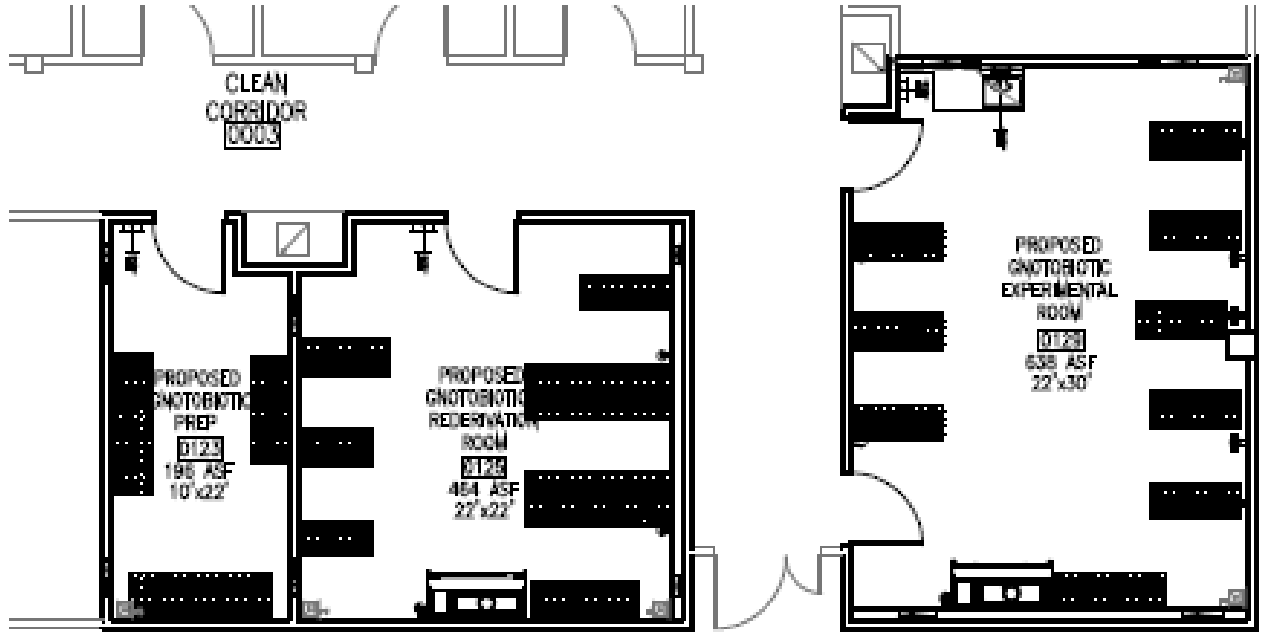
Variable region sequencing/alignment to database (targeted metagenomics)
- 16S rRNA (Bacteria & Archaea)
- ITS (internal transcribed spacer) rRNA (fungi)
- VLP purification & amplification (virus)

Functional Activity
- Shotgun metagenomics (putative)
- Metatranscriptomics (active pathways)
- Metabolomics

Integrative Pathway Analysis
Metabolites
Gene activity
Microorganism identification

Host-Microbe Interactions

Gnotobiotic Mouse Research Center *(Core B, Animal Care)*

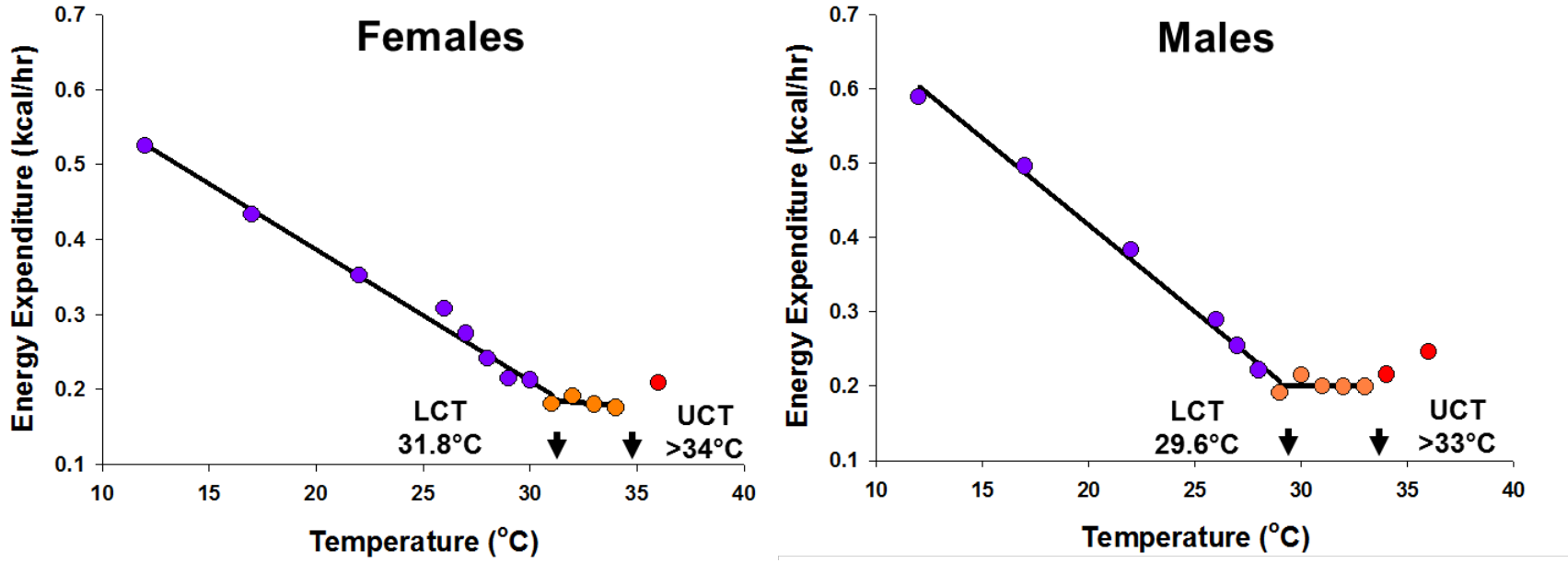


Facility Update:

- Enable experimental manipulation of gut microbiome
- Numerous services (rederivation, knockout/transgenic/Cas9 mice, diet)
- Capacity (340 cages: 100 rederivation/breeding, 240 microbial challenge)
- In-service July 2016

Temperature Challenge (Core D, Body Composition)

Enables one to determine how shifts in the thermoneutral zone or energy expenditure response to cold contribute to weight gain.



The relationship between ambient temperature and energy expenditure in male and female mice

Service Update:

- Determination of thermoneutral zone (lower and upper critical temperatures)
- Energy expenditure in response to cold or heat stress
- In-service 2015

Physical Activity (Core D, Body Composition)

Enables determination of the extent to which physical activity-related energy expenditure is altered in mouse models.

Calorimetry chamber with running wheel

Service Update:

- Energy expenditure measured with running wheel access
- Energy expenditure during treadmill running
- In-service 2015

Exercise *(Core E, Cardiovascular & Pathology)*

Starr Life sciences in-cage running wheels (20 wheels)

- Evaluate the effect of voluntary exercise
- Can be paired with other metabolic measurements (i.e. CLAMS, insulin sensitivity, DEXA)
- Measures: distance, speed, intervals of running
- Provide enrichment

Service Update:

- ➢ First cohort to be run in Feb 2016
- ➢ To be offered as service later 2016

Metabolomics (Core C, Endocrinology & Metabolism)

Fiehn

Adapting for small volume biofluids, low amount tissues

Metabolomics @ UC Davis

~ 1000-fold less organ tissue in mouse v. human

Liver 1.20 g in mouse → 1,561 g in human
Lung 0.13 g in mouse → 840 g in human
Heart 0.12 g in mouse → 300 g in human

~ 1000-fold less typical blood withdrawal

mouse < 100 ul → human 10 ml

increased sensitivity needed

micro-LC

reduce peak volume
→ more sensitivity

~ 5 fold more sensitive

high-recovery vials

reduce vial volume
→ more total sample injected

~ 3 fold less sample

ion mobility focusing

peak focusing like in electrophoresis

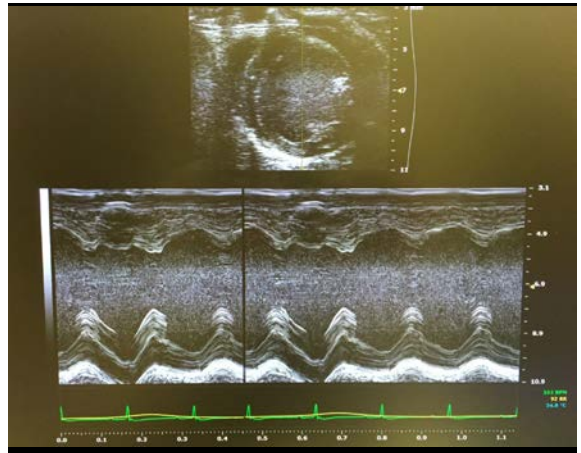
~ 10 fold better s/n

Echocardiography (Core E, Cardiovascular & Pathology)

- Non-invasive technique
- Able to detect:
  - Localized or generalized hypertrophy
  - Thinning of the myocardium of the left ventricle
  - Presence of regional or global wall motion abnormalities associated with systolic dysfunction
- Applications of transmittal Doppler analysis allows the detection of abnormal filling patterns associated with left ventral diastolic dysfunction

Service Update:

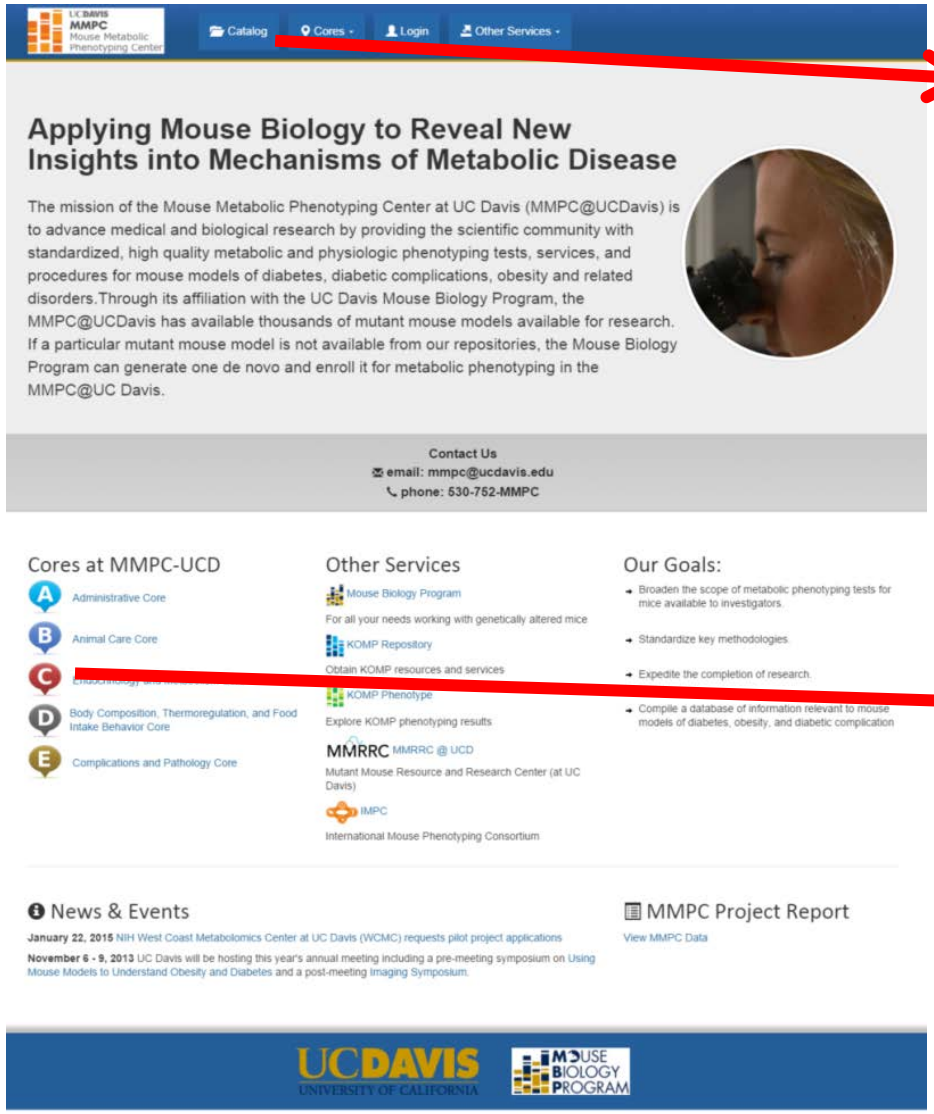
- ➢ Technicians trained
- ➢ LIMS established
- ➢ In-service Fall 2015

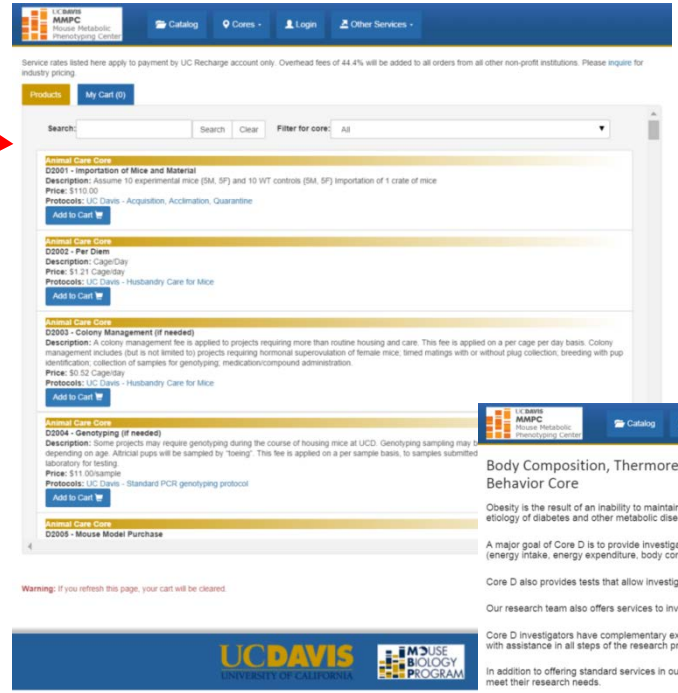


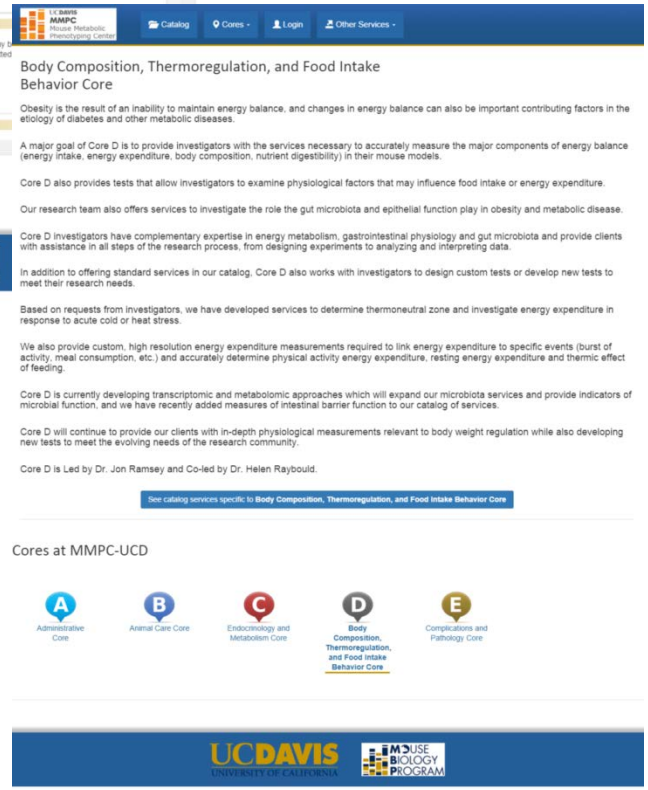
Parasternal Short Axis (PSAX)

Parasternal Long Axis (PLAX)

Website (Core A, Administration)





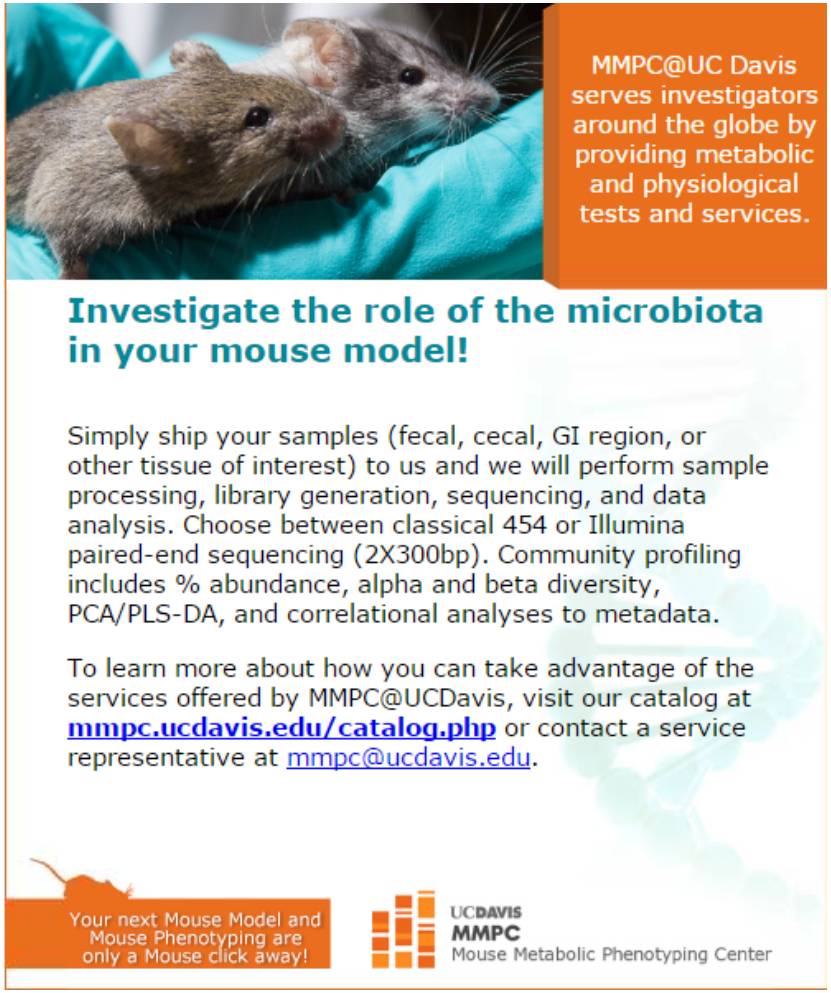


Y04 Metrics (Core A, Administration)

- ***Outreach campaign***
  Targeted e-mails sent to over 113,123 recipients
- ***Response Tracking for e-mail inquiries***
  230 message inquiries received since May '14
- ***Working Groups participation***
  Bariatric Surgery, Imaging, Energy Balance
- ***Catalog of UCD tests and services***
  91 services described online, 94% with SOP's
- ***Utilization since opening (October 1, 2011)***
  25 institutions, 92 client orders, 23,936 tests
- ***Publications linked to MMPC Grant#U24DK092993***
  43 with/10 without Center co-authorship

Y04 Outreach (Core A, Administration)

example of email flyer:



Targeted, bi-monthly e-mail campaign, 2014 - 2015

113,123 targeted e-mails sent covering the following topics

2014 (13,126 emails)

Metabolic Phenotyping of Dementia Mouse Models
Metabolic Phenotyping of Parkinson's Mouse Models
Metabolic Phenotyping of Alzheimer's Mouse Models
Metabolic Phenotyping of Stroke Mouse Models

2015 (99,997 emails)

Mouse Models of diabetes, obesity, or related disorders.
Mouse Models for Bariatric surgery
Gut Microbiome Analysis

mmpc@ucdavis.edu
mmpc.ucdavis.edu
855-UCD-MMPC (toll free)

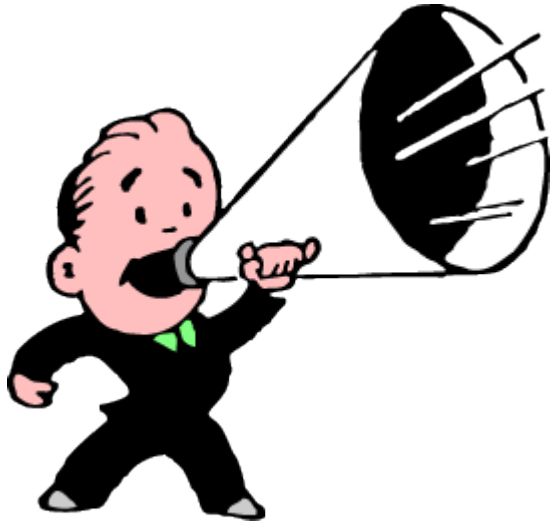
UCDAVIS MMPC
Mouse Metabolic Phenotyping Center

MMPC Mouse Metabolic Phenotyping Center

NIH U24 DK092993

also…

Rick McIndoe



ADMINISTRATIVE CORE	Samrrah Raouf Suzann Wadsworth Dave Clary Craig Warden Laurel Beckett
ANIMAL CARE CORE	Kristin Evans Stephen Griffey Kristin Grimsrud Christopher Pivetti Leslie Stewart Amy Kuhn Todd Tolentino
ENDOCRINOLOGY & METABOLISM	Peter Havel Fawaz George Haj Oliver Fiehn Mark Huising James Graham
BODY COMPOSITION, THERMOREGULATION, AND FOOD INTAKE BEHAVIOR	Jon Ramsey Helen Raybould Trina Knotts Charlotte Ronveaux
COMPLICATIONS AND PATHOLOGY CORE	John Rutledge Sue Bodine Dennis Wilson Nip Chiamvimonvat Jan Nolta Simon Cherry Amparo Villablanca Jennifer Rutkowsky