September, 2009

Evaluation Report to the NIDDK Advisory Council

Mouse Metabolic Phenotyping Centers

http://www.mmpc.org

Funding History

MMPC Centers
$3,000,000 funded by NIDDK
http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-00-014.html

July 1, 2006 – June 30, 2011
MMPC Centers
$4,200,000 funded by NIDDK, NHLBI and Special Appropriation for Type 1 Diabetes

MMPC and AMDCC Coordinating and Bioinformatics Unit
$1,000,000 funded by NIDDK, NHLBI and Special Appropriation for Type 1 Diabetes

Draft Timeline for Renewal

<table>
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<tr>
<td>RFA Published in Guide</td>
<td>Spring, 2010</td>
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<td>Application Receipt</td>
<td>Fall, 2010</td>
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<td>Council</td>
<td>May, 2011</td>
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I. Introduction

The ability of the scientific community to exploit the power of molecular biology for understanding complex diseases such as diabetes and obesity is limited by our ability to identify subtle changes in fat and carbohydrate metabolism, exercise and feeding behavior or organ function in the intact animal, due to their small size and the special expertise and equipment needed. The Mouse Metabolic Phenotyping Centers were designed to provide these complex physiologic and metabolic tests as services in order to phenotype mouse models beyond what would be possible or cost-effective in most labs. Therefore, the core goal of the MMPC is to develop, refine and standardize and apply a broad range of tests to phenotype knock-out mice and other mouse models of diabetes, obesity and their complications. The six MMPC Centers are housed at outstanding medical research institutions, run by top researchers, employ cutting edge technologies, and work closely together and with the Coordinating and Bioinformatics Unit (CBU) to serve the communities of academic researchers that use mice to study diabetes, obesity, and diabetes complications.

Each Center brings unique strengths to the consortium. The current strengths are in whole body carbohydrate and lipid metabolism; insulin action; fat absorption and digestion; cardiovascular function and pathology; kidney pathology; microvascular complications; body composition; energy balance and eating behavior; hormones and adipokine measurements; ion and nutrient measurements; and intermediary metabolic pathway characterization using NMR and mass spec isotopomer analysis (such as TCA cycle and gluconeogenesis flux).

The investigators at the Centers have agreed to share their expertise, creativity, technology and resources with their colleagues across the nation in the belief that this integrative team approach will significantly accelerate our knowledge of the role of different genes in diabetes and obesity and how these disorders are influenced by the interaction of these genes with the environment. The group shares technology via annual practical and classroom courses, and through the production of standardized protocols for popular tests. They compare and contrast different phenotyping technologies and carefully characterize the common background mouse strains used for transgenic models. They stimulate new technology development and evaluation, novel mouse metabolic research, and engage young researchers through two peer reviewed funding mechanisms. They bank the data acquired in hopes that the same tests, done by the same hands, in a large variety of mouse models, will add considerably to our understanding of diabetes and obesity. The MMPC functions as a consortium with an active Steering Committee representing the NIH and all Centers, and an External Evaluation Committee (EEC). Common guidelines have been designed, as well as a website, catalog of available tests, and database. The consortium has an established collaboration with the NIH-funded Animal Models of Diabetes Complications Consortium in order to help characterize new mouse models of diabetic complications.
II. Current Mouse Metabolic Phenotyping Centers

Phenotyping Centers

Case Western Reserve University, Henri Brunengraber, PI
http://www.case.edu/med/mmPC/index.html

University of Cincinnati, Patrick Tso, PI
http://mousephenotype.uc.edu/UC/index.htm

Vanderbilt University, David Wasserman, PI
http://www.mc.vanderbilt.edu/mmPC

University of Washington, Seattle, Renee Leboeuf, PI
http://www.mmPC.washington.edu/

Yale University, Gerald Shulman PI
http://mouse.yale.edu/

University of Texas, Southwestern Medical Center, Craig Malloy, PI
http://www4.utsouthwestern.edu/rogersnmr/mousepheno.htm

Coordination and Bioinformatics Unit (CBU)

Medical College of Georgia, Richard McIndoe, PI
http://www.mmPC.org
III. MMPC Response to 2004 Evaluation Recommendations

A midcourse evaluation was conducted in September of 2004. The suggestions from that report made by the External Evaluation Committee and Executive Steering Committee are found in Appendix A. Detailed here are the MMPC responses to these suggestions that were instituted between 2005 and 2009.

2004 Immediate Opportunities

1. Provide new ways to educate and train the community in order to improve metabolic and physiologic phenotyping in general. This has been an area of real focus of the MMPC in recent years, resulting in two lines of endeavor. Two annual week-long courses have been put in place that are taught by MMPC Center faculty and External Advisors. These are meant to inform the research community regarding the principles and practices behind in-depth metabolic phenotyping, and enable researchers to incorporate the types of phenotyping done in the MMPCs into their own laboratories. The MMPCs have also worked very hard to document best practices for the more complex tests, explore the impact of various parameters, compare data from background strains, and do head-to-head comparisons of different technologies designed to measure similar phenotypes (for instance, doubly-labeled water and indirect calorimetry to measure energy balance.). These efforts are resulting in a series of peer-reviewed papers that serve to establish best practices and inform the mouse research community about them, and advertise the MMPC services.

2. Provide “bang for the buck” to MMPC clients by improving ability to do several tests on each mouse. While difficult to address, the MMPC has explored a number of ways to improve the efficiency of phenotyping and reduce the cost to the client and Center. The MMPCs have added noninvasive body composition, eating behavior, activity, fat absorption, and energy balance tests that can be done prior to invasive tests that end in sacrifice. This has required purchase of expensive equipment and therefore there has been slow but steady progress. An enormous barrier is the need for quarantine and inability to return live mice to the institutional vivaria after non-invasive tests. The MMPCs have tried to relieve this constraint. One way is to have mice shipped directly from ‘clean’ vendors. Other measures include siting MR-based machines for non-invasive measures of body composition in the animal rooms, building MMPC-dedicated animal rooms near the testing sites, and the use of mobile animal barriers where the animals can be housed and wheeled among testing cores. The MMPC has also added tests that do not require animal shipping; for instance, the client can infuse stable isotope tracers at home, and ship plasma and tissues to the Centers for flux analysis of metabolic pathways. In some cases, mice have been tested and shipped home to the originating lab.

2004 Other Suggestions

3. Increase capacity for popular tests, make sure capacity for other tests is appropriate. The most popular tests are plasma hormone and metabolite assays. There are now very active cores, that use similar or identical assays, at several MMPCs, and the capacity to measure lipids has substantially improved. The MMPCs have made steady progress toward instituting the insulin clamp at additional sites (Cincinnati and Case).
4. **Improve websites, focus on the perception of service to the community.** The website [www.mmpc.org](http://www.mmpc.org) has been vastly improved and the service aspect of the MMPC made far clearer. Access to test descriptions and an online test order module has removed many barriers. The individual Center websites are improved and better maintained. The CBU continues to provide new web based tools that improve interaction between the MMPCs and the client community.

5. **Make the fee structures more uniform.** Progress has been made, whereby many tests are offered for about 60% actual cost. It is complicated by differing University business practices and local labor costs, etc., which lead to very different costs for similar tests at different MMPCs. Another problem is the fact that a few of the tests offered are extremely labor and machine-intensive, resulting in prohibitive charges when they are calculated by formula. The different tests have very different ‘success rates’, which must be taken into account when setting prices. Others are in earlier developmental stages where each experiment is somewhat different and therefore requires a lot of staff time and input. The MMPCs continue to work toward the goal of a uniform fee structure.

6. **Provide more detail in documented protocols for all tests in the catalog—perhaps in papers.** The MMPC took this suggestion seriously and has more thoroughly documented test protocols on the web and in the Catalog of Services, and through publication of papers focused on ‘best practices’ for complex tests. Currently, subcommittees are working on standard operating procedures (SOPs), intended for peer reviewed publication, in scientific areas where multiple MMPCs have cores (carbohydrate metabolism, energy balance, cardiovascular). In the same spirit, the very thorough manual written to accompany the Vanderbilt mouse clamping course has been published on the website and is available for everyone at [http://www.mc.vanderbilt.edu/root/pdfs/mmpc/Manual/MMPC.pdf](http://www.mc.vanderbilt.edu/root/pdfs/mmpc/Manual/MMPC.pdf).

7. **Improve advertising.** The MMPC has tried to improve advertising via vastly improved websites, organizing symposia, and the use of posters at large meetings such as the ADA and AHA, as well as distribution of brochures. Although it is difficult to judge the efficacy of these efforts, there does appear to be a fairly widespread knowledge and use of the MMPCs currently. The MMPC continues to work on this.

8. **Improve the characterization of obesity.** This is an exciting and somewhat daunting goal given the speed of obesity research in the last several years. The MMPC has improved its ability to measure body composition, energy balance, eating and locomotor behavior, insulin resistance, adipokine analysis, meal fat absorption, lipid turnover and synthesis, acyl-CoA and other associated molecules, and hypothalamic gene expression. The MMPC is working currently to add the ability to make a variety of mouse models of bariatric surgery. Improvement in this area is ongoing.

### 2004 Future Needs

9. **Establish an independent coordinating center.** The MMPC and AMDCC now share a coordinating and bioinformatics unit.

10. **Scientific needs: monitor core body temperature and metabolic rate over time.** The Cincinnati and Case MMPCs now have the ability to monitor body temperature with telemetry. Most of the MMPCs now have metabolic cages to monitor metabolic rate,
and with the addition of the Case MMPC, the ability to monitor energy balance over time with doubly labeled water has been added.

11. **Scientific need: comprehensive tests to phenotype complications of diabetes, esp. neuropathy.** The collaboration with AMDCC has resulted in the addition of the Washington MMPC with focus on cardiovascular, kidney complications and retinopathy. This MMPC works with AMDCC and the JAX labs to phenotype new models of complications as they are produced. The Vanderbilt MMPC has developed a hypoglycemic clamp to explore the metabolic picture of hypoglycemia unawareness in diabetes. The MMPC and AMDCC organized a symposium focused on phenotyping retinopathy and neuropathy, and solicited and funded several P&F projects in this area. The funded investigators continue to work with the AMDCC to improve technology.

12. **Scientific need: core focused on eating behavior, activity and energy balance.** The MMPC has vastly improved its number of metabolic cages, and the Washington MMPC has a focus on technology development in this area.
IV. Description of the NIDDK MMPC Program

A. Mission and Goals
The MMPC mission is to advance medical and biological research by providing the scientific community with standardized, high quality metabolic and physiologic phenotyping services for mouse models of diabetes, diabetic complications, obesity and related disorders.

MMPC Goals:
1) broaden the scope of metabolic phenotyping tests for mice available to investigators;
2) standardize key methodologies;
3) expedite the completion of research;
4) assist young investigators or established investigators in other fields in diabetes and obesity research; and
5) compile a database of information relevant to mouse models of diabetes, obesity and diabetic complications.

B. NIH Funding
Four MMPC Centers were awarded for the first 5 years with $3,600,000 per year of NIDDK funds. In 2006, the MMPC program was expanded. NIDDK contributed $3,700,000; NHBLI joined and contributed $300,000 per year; and a collaboration was formed with the Animal Models for Diabetes Complications Consortium (AMDCC) which contributed $900,000 per year to the MMPC for tests for diabetic complications. The AMDCC is funded through the Special Appropriation for Type 1 Diabetes Research. In 2007, the NIDDK added $450,000 per year for an annual competitive research funding program (the MICROMouse program). The total NIH funding for the MMPC in years 6-10 is therefore $5,350,000 annually.

These funds are currently used for six MMPCs ($4,229,407 total costs) and a Coordinating and Bioinformatics Center (CBU). The CBU ($1,924,735 total costs) is shared by the AMDCC and the MMPC, and includes funds for the MMPC Pilot and Feasibility (P&F) ($280,040) and MICROMouse funding programs ($450,000) and the AMDCC Pilot and Feasibility funding program ($460,010). The CBU annual operating budget ($734,685 total costs) funds coordination and travel for the Consortia meetings, and the MMPC and AMDCC websites and databases.

C. Center Structure and Business Plan
Each Center has a structure that consists of an Executive Committee, an Administrative Core and Director, experimental and analytical Test Cores, an Animal Health and Welfare Core, and a Research & Development program. The MMPC program has a Coordinating and Bioinformatics Unit which houses the MMPC Pilot and Feasibility grant program, the MMPC website, and MMPC Database. This CBU is shared with the NIH-sponsored Animal Models of Diabetes Complications Consortium (AMDCC). Details for the structure and personnel at each MMPC can be obtained from the individual web sites. The six Centers share a National Steering Committee consisting of Center Directors, NIH personnel, and external advisors.

Each Center has its own business plan and business rules, designed in compliance with guidelines set up by the National Steering Committee and the NIH funding Institutes.
The business plans are tailored to meet the needs of the parent academic institution, the laboratory and the specific tests offered. In general, test cores are expected to receive and evaluate applications for services, log orders into the shared database, conduct tests, enter the resultant data into the shared database and deliver data to the users, establish subcontracts or bill for services and collect payment, and release data to the public when appropriate. Core directors also advise users regarding appropriate tests and write letters of support for grant applications. Fees are expected to cover 40-60% of the costs of the tests, and program income can be spent on core personnel, equipment and supplies. In special rare cases where substantial intellectual effort from MMPC staff is involved, the MMPC can fund tests as collaborative projects with outside MMPC users.

D. National Steering Committee
This committee is chaired in annual rotation by the Center Directors. It meets by phone each month and in person annually in September with the Advisory Board at the Chair’s institution. This allows for all MMPC members to visit each Center in turn over time, and for all Center staff to attend the entire annual meeting occasionally. It is composed of the Center and CBU principal investigators, core directors, administrative assistants, AMDCC members, advisors and NIDDK program staff. This body creates guidelines, sets priorities and policies, designs collaborative activities, oversees the websites, database, and the Pilot and Feasibility and MICROMouse funding programs, and establishes subcommittees to carry out joint activities. Although it oversees administrative issues having to do with the MMPC, its focus is on establishing scientific priorities and paving the way for scientific advances. The level of cooperation and collaboration among the members of the MMPC Steering Committee must be considered an outstanding success. The CBU provides infrastructure, coordination and travel funding in addition to its bioinformatics support and research. The minutes of the Fall 2008 National Steering Committee meeting, held in Seattle, WA are included as Appendix B.

E. Advisory Board (2006-2010)
The seven members of the advisory board provide advice with regard to all aspects of the MMPC. They participate in review and selection of MICROMouse and P&F grants, and in design and teaching of annual courses. They attend the annual fall meeting and help set guidelines and the agenda for the coming year, and evaluate the need for existing or new tests, equipment and cores. In order to become familiar with the details of the program and prepare for the 2009 evaluation that produced this report, each advisor visited an MMPC in summer of 2008.

<table>
<thead>
<tr>
<th>Joseph Nadeau, Ph.D.</th>
<th>Thomas W. Gettys, Ph.D.</th>
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<tr>
<td>Chair &amp; Professor of Genetics</td>
<td>Professor &amp; Chief</td>
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<tr>
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<td>Pennington Biomedical Research Center</td>
</tr>
<tr>
<td>Department of Genetics</td>
<td>Division of Experimental Obesity</td>
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<tr>
<td>10900 Euclid Avenue</td>
<td>6400 Perkins Road</td>
</tr>
<tr>
<td>Cleveland, OH 44106-4955</td>
<td>Baton Rouge, LA 70808</td>
</tr>
<tr>
<td>Phone: 216-368-0306</td>
<td>Phone: 225-763-3165</td>
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<tr>
<td><a href="mailto:ihn4@po.cwru.edu">ihn4@po.cwru.edu</a></td>
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<tr>
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<td><a href="mailto:gettystw@pbrc.edu">gettystw@pbrc.edu</a></td>
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In addition to consulting the advisory committee, the MMPC employs outside peer review whenever possible. NIH funding for the MMPCs is peer reviewed of course, but also all MMPC research funding programs use external peer review, courses are funded through peer-reviewed NIH sponsored programs, and all MMPC consortia publications are published in peer reviewed journals. All this serves to maintain high quality, engage the community intellectually with MMPC activities, and advertise the MMPC services.

F. Collaboration with the AMDCC for Phenotyping of Diabetes Complications

The AMDCC ([www.amdcc.org](http://www.amdcc.org)) is an NIH-funded interdisciplinary consortium designed to develop new animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention and treatment. Additional goals of the AMDCC are to define criteria to validate each of the diabetic complications in mice for its similarity to the human disease, test the role of candidate genes that emerge from human genetic studies, and facilitate the exchange of models, tissues, reagents, and expertise between members of the consortium and the greater scientific community. The consortium consists of thirteen "pathobiology sites" that study complications such as diabetic nephropathy, uropathy, neuropathy, cardiomyopathy and vascular disease. The AMDCC and MMPC share the CBU as well as website and database architecture.
The AMDCC works with the Jackson Laboratories to create and do initial phenotyping of new mouse models of complications. Promising models of a particular complication such as nephropathy are then sent to the MMPC for additional complications testing in other organ systems, and for more intensive metabolic phenotyping.

G. The MMPC Website (www.mmpc.org)

The MMPC website serves as the nexus for the MMPC core descriptions and personnel, test catalog, ordering process, guidelines and contacts, subcommittees, courses, literature, database and the interface and statistical tools for using data. It also has a password protected members only area which houses meeting minutes, member information, test order information, and funding program administrative activities. mmpc.org was designed and created at the CBU, and is also housed and maintained there. In addition to the main MMPC website, each Center maintains its own website with specific information. For more information, see section V.G.

H. Catalog of Available Tests

Centers were asked to design or adapt and standardize a variety of tests that can be conducted on living mice or on body fluids and tissue samples. Mice are expected to have obesity, insulin resistance, abnormal glucose and lipid metabolism, mitochondrial and other organelle-specific defects, altered circadian, feeding and locomotive behavior, altered fat storage, nutrient oxidation or energy balance, defective hormonal or cytokine action and intracellular signaling, or altered susceptibility to the complications of diabetes. Centers each specialize in specific areas, but most share some core abilities, such as body composition and hormone, nutrient and ion measurements. Technologies include glucose and insulin clamps, confocal and whole body imaging, NMR spectroscopy, mass spectrometry, stable and radioactive tracers for pathway fluxes, EKG and EEG, histopathology, radioimmunoassay, indirect calorimetry, etc.

A searchable online catalog of more than 220 available tests and their descriptions is found at http://www.mmpc.org/shared/catalog.aspx, and a .pdf version is found in Appendix I. The costs are posted at the specific Center websites. Tests can be selected by Center, core or by keyword. In addition to these tests, the Centers often design more tailored tests in response to specific needs of the applicant investigators. The tests tend to fall into the following categories:

<table>
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<tr>
<th>Amino Acid Metabolism</th>
<th>Body Composition</th>
<th>Carbohydrate Metabolism</th>
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<tr>
<td>Cardiac Function</td>
<td>Central Nervous System</td>
<td>Circulation</td>
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<tr>
<td>Diabetes</td>
<td>Energetics</td>
<td>Energy Expenditure &amp; Exercise</td>
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<tr>
<td>Enzymatic Activity</td>
<td>Food Intake</td>
<td>Hormone Measurements</td>
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<tr>
<td>Imaging</td>
<td>Immunology of Diabetes</td>
<td>Insulin and Insulin Function</td>
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<tr>
<td>Isolated Organ and Cell Perfusion</td>
<td>Kidney Function</td>
<td>Lipid Metabolism</td>
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<tr>
<td>Liver Function</td>
<td>Metabolite Concentration and Enrichment</td>
<td>Modeling and Simulation</td>
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<tr>
<td>Magnetic Resonance Spectroscopy &amp; Imaging</td>
<td>Pancreas, Islets and Beta Cells</td>
<td>Pathology &amp; Immunohistochemistry</td>
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<tr>
<td>Surgery</td>
<td>Vascular Function</td>
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After identifying the appropriate Center(s) from the individual web pages or test catalog the applicant should first contact the Center Director or Core Director to discuss the mouse strain, determine the best set of tests to be conducted, and obtain an estimate of costs. The applicant then obtains a password protected account and completes an online request for services which is targeted to the appropriate Center. The request is reviewed by the Center Executive Committee. Acceptance is based on Center workload, relevance of the available and/or requested tests to the mouse model, and the perceived value of the animal to diabetes, obesity, and metabolic disease research. The applicant will be contacted with the decision. Following consultation with the Center and/or Core Director(s), a written estimate for all tests agreed upon, including the number of mice required for each test and a timeline for receipt and testing of the mice at the MMPC, will be sent to the applicant for his/her approval. Upon completion of the requested tests, data in an appropriate form will be stored in the MMPC database and posted on MMPC's password protected web site for viewing by the submitting investigator only. The Center personnel will be available to discuss experimental details, etc.

I. Policies and Guidelines for Users


- All data generated from a submitted strain belongs to the submitting investigator and his/her institution.
- Center personnel have no rights to use this data for personal or institutional research purposes unless a formal, documented arrangement of collaboration exists between Center personnel and the investigator.
- The NIH strongly encourages the sharing of research data. NIH guidelines regarding data sharing can be found at [http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html](http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html).
- In particular, users are requested to allow the data generated in the MMPC to become publicly available (via the MMPC database) after the first of the following two conditions has been met: a. the data have been published and are therefore in the public domain; b. two years have passed since the investigator received the data from the Center.
- The Center personnel and the investigator must read and sign a Mouse / Tissue Transfer Agreement, which clearly states these rights and responsibilities.

J. Animal Care and Shipping
A Subcommittee on Animal Husbandry Issues, comprised of Center Animal Core Directors and veterinarians, designed a common procedure for shipping, receiving, housing, feeding, quarantine, and a common list of pathogens for which all animals are tested prior to and after shipping. These are detailed at https://www.mmpc.org/shared/animalShipping.aspx

K. The MMPC Database

The phenotyping data acquired by the MMPC will be a valuable resource for the diabetes and obesity research community by virtue of the fact that these data will have been obtained using the same protocols, by the same researchers, using the same equipment, and are therefore directly comparable across a variety of knockout and transgenic strains. The MMPC database is housed, designed and maintained at the CBU and can be accessed via the MMPC website at https://www.mmpc.org/shared/search.aspx. Center personnel organize and track mice and tests in the administrative portion of the database. Numerical data is entered into the database on site directly from each MMPC core, and is transmitted to the client via a password protected section of the database. The CBU is working to be able to include other forms of data, such as histopathology, confocal or MR images, or NMR and mass spectra. Data is tracked and released to the public once published or when two years have passed since test completion. For more information, see section V.G.

L. Funding Programs

Pilot and Feasibility Program
The development of new techniques and tests for the metabolic characterization of mice is a crucial component of the MMPC and the Pilot and Feasibility Program is key to promoting such activities. Funding for these projects is competitively awarded each year to: 1) develop new technologies or miniaturization of existing technologies for use in mice, 2) development of applications of existing technologies for use in mice, 3) provide new tests to meet identifiable, outstanding needs of the Center, 4) establish new types of mathematical models, informatics, databases or products that augment the mission of the center. It is not the intention for these funds to augment ongoing funded research of an investigator and in most cases the funding is not renewable.

The CBU is responsible for the implementation of the Pilot and Feasibility Grant Program. This includes the request for applications, review process, and budget management. Second level of review and final funding decisions will be made by the MMPC Steering Committee at its annual meeting. A summary of progress of funded projects is due two months following the completion of the funding period (November 30 of the year following the start of funding). A list of funded studies is found in section VI.E.

MICROMouse
The MMPC has set aside $450,000 annually for small short-term grants (up to $75,000 total costs per year) to fund collaborative biomedical research projects between an MMPC and external investigators, or among MMPCs. Applicants can be from any research institution. Proposal objectives should take clear advantage of collaborations with MMPCs to address
questions that would be otherwise difficult to answer. MICROMouse proposals should be research-driven rather than focused on test development. Applications should explicitly address how the proposal is distinct from the current grant support of principal investigators and that this funding is not taking the place of typical MMPC user fees. Examples of suitable proposals include but are not limited to 1. the pursuit of novel questions formed during routine phenotyping of animals in collaboration with the submitting investigator; 2. thorough phenotyping of new models that may be important for the study of a variety of diseases, but are outside the scope of the submitting investigator’s funding; 3. to bring together investigators with complimentary mouse models that would not normally interact; 4. collaboration between Centers to validate methodology important for mouse studies, but that do not meet the qualifications of the MMPC P&F program; 5. investigation of new molecular targets uncovered by prior MMPC studies. Objectives should be reasonably met within the one year funding period and lead naturally to publication and potential NIH funding.

There is no application deadline, and applications are reviewed and selected for funding four times per year. Each submitted proposal is assigned to three reviewers who are either members of the MMPC External Advisors or external scientists with expertise in the area of a proposal. Second level of review and the final funding decisions are made by the MMPC Steering Committee. Proposals may be submitted only once for funding consideration unless a revised application is solicited by the MMPC Steering Committee. Applications for competitive renewal (1 additional year) are encouraged in cases where exemplary progress has been made and further investigation is warranted. A list of funded studies is found in section VI.E.

M. Courses and Outreach
In addition to making phenotyping technology widely available to academic research laboratories through the fee for service test cores, the MMPC also works to educate researchers and translate phenotyping technology into other laboratories by conducting annual courses and special symposia.

Glucose Clamping The Conscious Mouse: A Laboratory Course
http://www.mmpc.org/shared/clamping.aspx
The Vanderbilt MMPC holds an annual week-long hands-on practical course in Nashville, TN, to familiarize participants with methods, protocols and quantitative tools necessary to perform glucose clamps in the conscious mouse. Ten students are trained per year, and on August 31-September 4, 2009, the fifth annual course will be held.

Isotope Tracers in Metabolic Research: Principles and Practice of Kinetic Analysis
http://www.mmpc.org/shared/tracers.aspx
A week-long, team-taught annual course in the theory and practice of isotopic tracers (stable and radioactive) for the study of metabolism in man and animals using mass spectrometry and NMR. The course emphasizes isotopomer analysis for metabolic flux rates and metabolic regulation. This course is sponsored by MMPC and a competitively funded grant, R25 DK082376, from NIDDK to H. Brunengraber.

An Organ Systems Approach to Experimental Targeting of the Metabolic Syndrome
http://www.mmpc.org/shared/metabolicSyndrome.aspx
This course not specifically under the auspices of the MMPC although several MMPC faculty from inside and outside Vanderbilt participate in teaching. It is hosted by the Vanderbilt University School of Medicine in Nashville, TN, and the first meeting was held on July 20-31, 2009. It is an intensive two week experience for 20 students. The objective of the course is to give students the tools needed to assess whether an experimental intervention (pharmacologic, genetic, dietary, or environmental) alters macronutrient metabolism, energy balance, cardiovascular homeostasis or animal behavior. The course entails a combination of lectures, hands on laboratories, demonstrations and data problem sessions. This course is sponsored by a competitively funded grant, R25 GM086771, to O. McGuinness.

The MMPC and the AMDCC collaborated to organize a two day symposium, Advances Toward Measuring Diabetic Retinopathy and Neuropathy: from the bench to the clinic and back again, April 4-5, 2007 in Baltimore, MD, and to fund pilot and feasibility studies focused on novel technologies to phenotype neuropathy and retinopathy in mouse models of diabetes (see above).

MMPC members held a special symposium at the 2008 annual American Heart Association Scientific Sessions in New Orleans, entitled "How to Phenotype Mouse Models with Metabolic Diseases".

N. Advertising
The MMPC advertises through distribution of brochures and other literature and occasional posters at major meetings such as the American Diabetes Association and the American Heart Association (see Appendix H), and through the NIDDK and MMPC websites. Courses are advertised through email and websites.
IV. Center Description and Progress

This report is intended as an evaluation of the overall MMPC program and is not meant to focus on the individual Centers. However, the six Centers and the CBU are described below, along with summarized data regarding their use. Each Center was also asked to fill out a survey regarding its business plan, and these are included in Appendix F. Appendix C contains criteria that were vetted by the MMPC National Steering Committee as ‘benchmarks of success’ for the Centers and the MMPC program.

A. MMPC at Case Western Reserve University
http://www.case.edu/med/mmpc/index.html

A1. Brief Center Description
The Case MMPC was first established in 12/2006. The primary focus is on whole body metabolism and energy balance, and measurement of intermediary metabolism fluxes using stable isotopes and mass isotopomer analysis assayed by mass spectrometry. These include rates of lipid turnover, amino acid and protein turnover, carbohydrate metabolism including gluconeogenesis and glycogen. The Center also does a wide range of metabolite analysis, including acyl-CoAs and a variety of lipid metabolites. Center staff has been very involved in MMPC administrative activities, in collaborative research projects, and in developing and teaching MMPC courses.

Center Director: Dr. Henri Brunengraber
Administrator: Laila Boesinger
Animal Core Director: John Durfee
Quarantine: 6 weeks
2009 Award: $345,000 direct costs (awarded as subcontract from CBU)
MMPC established December, 2006

A2. Self-Reported Data Statistics
The following numbers represent use of the cores reported in annual progress reports to the NIDDK

Program Income Reported: Year -08 April, 2009: $ 50,500
Year -07 April, 2008: $ 23,603
Year -06 April, 2007 $1,338

The Case MMPC is experiencing a major increase in business volume and user number since March 2009. A number of new users contacted us during and after the course on isotope techniques (May 2009).

Published Papers referencing DK076169*: up to 22 papers total, 6/06 – 7/09 (Pubmed)
Annual reports April, 2009: 1 paper, 4 abstracts (all Case)
April, 2008: 2 papers (all Case)
April, 2007: 0 papers
Tracking papers published with data provided from the MMPCs remains difficult as not all users remember to acknowledge the grants or the Centers. DK76169 currently funds the Yale, Case, UTSW and CBU (MCG) MMPCs. Papers listed as ‘Case’ have at least one author from Case MMPC but many are written by external MMPC users.

**Metabolic Core**
Core Director: Colleen Croniger
Core Co-Director: Henri Brunengraber and Michelle Puchowicz
Staff: research assistants Frederick Allen, Todd Miker (to be replaced by Lan Wang 9/1/09; Lan is currently training with Todd and Fred)
Major Tests: Chronic or acute arterial, jugular and/or gastric catheterization, Acute catheterization of portal vein or urinary bladder, Energy expenditure by the "doubly-labeled water", Rates of fatty acid, cholesterol, triglycerides, or protein synthesis measured using $^2$H$_2$O, Insulin clamp, pancreatic clamp, Food intake, Glucose tolerance test, Body temperature, heart rate and activity monitored by telemetry, Urine and blood chemistry analysis, Glycosylated hemoglobin, Liver perfusion and heart perfusion, Tissue perfusion and fixation, brain blood flow, substrate uptake by the brain.

# 2008 6 Users: (6 Case)
# 2008 Orders: 6
# 2008 animals: 229 mice, 107 rats

# 2007 Users: 10 (6 Case, 4 outside)
# 2007 Orders: 10
# 2007 animals: 246 mice, 108 rats

# 2006 Users: 8 (7 Case)
# 2006 Orders: 8
# 2006 animals: 13 mice, 35 rats

**Analytical and Metabolomic Core**
Core Director: Michelle Puchowicz
Co-Directors: Henri Brunengraber
Staff: Paul Miller + Edwin Vasquez (in training)
Major tests: $^2$H- and $^{18}$O-enrichments of plasma or urine for total energy expenditure, protein synthesis, $^2$H-enrichment of plasma or urine for calculating total body water, turnover of glucose and/or glycerol with [6,6-$^2$H$_2$]glucose and [$^2$H$_3$]glycerol, Concentration and/or labeling pattern of plasma fatty acids (C$_8$-C$_{22}$), Concentration and/or labeling pattern of plasma amino acids, Concentration and/or labeling pattern of acylcarnitines in plasma or urine, Concentration and/or labeling pattern of long-chain acyl-CoAs in tissues, Concentration and/or labeling pattern of acetyl-CoA, propionyl-CoA, succinyl-CoA, and methylmalonyl-CoA in tissues, Concentration and/or labeling pattern of citric acid cycle, gluconeogenic intermediates and amino acids in tissues, $^{13}$C-labeling pattern of the acetyl moiety of citrate, activity of acetyl-CoA carboxylase or malonyl-CoA decarboxylase in tissues, rates of FA and cholesterol synthesis in tissues from the incorporation of $^2$H or $^{13}$C, rate of protein synthesis
from the incorporation of $^2$H-enriched water, metabolomic profile in plasma, urine or tissue,
Profile of 120 organic acids in urine,

# 2008 Tests: >1000 (50% from users inside Case)
Conducted hands-on training for 2 external clients (SUNY, Texas A&M).

# 2007 Users: data combined with that of Metabolic Core, see above

# 2006 Users: data combined with that of Metabolic Core, see above

**A3. Case MMPC Database Statistics**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>13</td>
</tr>
<tr>
<td>Completed Orders (database)</td>
<td>20</td>
</tr>
<tr>
<td>Orders with payment</td>
<td>17</td>
</tr>
<tr>
<td>Unique Investigators</td>
<td>13</td>
</tr>
<tr>
<td>Orders with data associated (database)</td>
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<tr>
<td>Phenotype Assays (database)</td>
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</tr>
<tr>
<td>Assay Measurements (database)</td>
<td>0</td>
</tr>
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<td>Animals (database)</td>
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</tr>
<tr>
<td>Strains (database)</td>
<td>0</td>
</tr>
<tr>
<td>Publications (database)</td>
<td>0</td>
</tr>
</tbody>
</table>

**These numbers represent the data entered into the database, but in most cases do not accurately represent the workload of the Center. They serve as a measure of compliance with data entry guidelines.**

A4. Tests Available at Case MMPC:
Please see [http://www.mmpc.org/shared/catalog.aspx](http://www.mmpc.org/shared/catalog.aspx)

A5. Progress in Technology at the Case MMPC
The Case MMPC has established the glucose clamp technique and the brain uptake index technique. The intracerebroventricular infusion technique is in development. The ovarian transplant technique (an ovary from a mouse with gene-targeted deletion transferred into wt mouse to study effect of maternal environment). Indirect calorimetry and ‘doubly labeled water’ methods for measuring energy balance have been compared in collaboration with Cincinnati and Seattle MMPCs.

A6. Case MMPC Business Plan Survey
See appendix F.

A7. Case MMPC Spotlight on Careers
The MMPC faculty interacts with many users and with faculty from other MMPCs. They benefit from discussions on development and use of techniques and protocols. They also increase their knowledge in fields of science adjacent to their own. This can help them widen the scope of their own research. It is true that MMPC faculty spend much time training users in developing protocols, interpret data, and avoiding artifacts. These time-consuming
activities often do not lead to orders to the Case MMPC and subsequent income. However, these activities are part of the educational mission of the MMPC network. The same can be said of the course on the use of isotopes for metabolic studies in which faculty from Case and other MMPC spend much time and effort (without income to the MMPCs and contribution to most course faculty salary). Lastly, getting a fraction of one’s salary covered by the MMPC grant helps the status of the faculty in her/his institution.

A8. Directors’ Comments

The perception of the time commitments to users (mentioned in the previous paragraph) as positive or negative depends very much on the personality and mindset of the individual faculty. MMPC faculty should be dedicated to all missions of the MMPC network, or should pursue other avenues. Natural selection helps in solving some discordance between the faculty’s view of professional life and the MMPC mission.

The current Case MMPC faculty does not seek authorships on papers reporting studies conducted by users with our help.

A9. Case MMPC Research Highlights


Abstracts


B. MMPC at University of Cincinnati
http://mousephenotype.uc.edu/UC/index.htm

B1. Brief Description of University of Cincinnati MMPC
The MMPC is a full service Center funded since 2000. The main focus is on lipid metabolism with unique services being the lymph fistula mouse, fat absorption and lipoprotein/cholesterol metabolism, fatty acid, triglyceride and other lipid turnover. The MMPC also offers tests in cardiac and kidney function, and in energy balance, eating behavior, expression of brain peptides, and body composition. Cincinnati MMPC staff members have been particularly active in laying the administrative and procedural guidelines for the consortium, in collaborations with other Centers and in the funding programs, and have been successful in establishing novel tests.

Center Director: Dr. Patrick Tso
Co-Director: Stephen Woods
Administrator: Dana Lee
Animal Core Director: Philip Howles
Quarantine: 8 weeks
2009 Award: $570,947 direct costs
UC MMPC established July, 2000

B2. Self-Reported Data Statistics
The following numbers represent use of the cores reported in annual progress reports to the NIDDK

Program Income Reported:  
Year -08 April, 2009:  $116,584  
Year -07 April, 2008:  $135,127  
Year -06 April, 2007 $134,000

Papers DK059630*:   50 papers total (Pubmed, 6/06-7/09)  
Annual reports  
Year -08:  25 papers (21 UC MMPC, 4 outside)  
Year -07:  23 papers (14 UC MMPC, 9 outside)  
Year -06:  11 papers (6 UC MMPC, 5 outside)  

*Tracking papers published with data provided from the MMPCs remains difficult as not all users remember to acknowledge the grants or the Centers.

Letters for grant applications: Year -08:  19 (11 UC, 8 outside)  
Year -07:  15 (4 UC, 11 outside)  
Year -06:  16 (16 outside)

Core C: Lipid, Lipoprotein, and Glucose Metabolism Core
Core Directors: Patrick Tso and David D’Alessio
Other Faculty: Laura Woollett, Ronald Jandacek
Staff: 2 full time research associates (Qing Yang, Danwen Lou)
Major Tests: Lipid profiles, intestinal lipid absorption, chylomicron metabolism, cholesterol synthesis, plasma hormones, lymph fistula animals, glucose, insulin, triglycerides, fatty acids
and other lipids, non-invasive measurement of fat absorption, CCK, C-peptide, GIP, GLP-1, and apolipoproteins.

# 2008 Users: 32 (11 UC, 21 outside institutions, including 3 from industry, 1 overseas)
# 2008 Orders: 46
# 2008 tests: 3141

# 2007 Users: 27 (12 UC, 15 outside)
# 2007 Orders: 47
# 2007 tests: 2741

# 2006 Users: 30 (11 UC, 19 outside)
# 2006 Orders: 40
# 2006 tests: 3306

Core D: The Cardiovascular and Renal Function Core
Core Director: David Hui
Staff: 1.3 research associates (Jody Caldwell, Eddy Konaniah)
Major tests: Specializes in blood pressure, blood flow, cardiac function, renal function parameters that can be affected by diabetes and/or obesity. Measurements are made in the intact animal or isolated heart and kidney.

# 2008 Users: 3 (1 UC, 3 outside institutions)
Tests conducted: assessment of atherosclerosis, assessment of vascular contractility, echocardiography, arterial blood pressure, heart rate, lipoprotein concentrations

# 2007 Users: 5 (2 UC, 3 outside institutions)
Tests conducted: lipid response to oral triglyceride load; assessment of atherosclerosis, neointimal hyperplasia in vessel wall

# 2006 Users: 2 (0 UC, 2 outside institutions)
Tests conducted: exercise and cardiac contractility, lipid and cholesterol profiles
Trained 2 postdoctoral students from other labs in exercise, cardiac contractility, and arterial injury tests. Both students visited several times for 2 days each in order to take these technologies back to their parent laboratories.

Core E: The Food Intake, Metabolism, and Body Weight Regulation Core
Core Director: Randy Seeley and Stephen Woods
Co-PIs: Randall Sakai, Matthias Tschoep
Staff: 1.1 FTE research assistants (Kathleen Smith, Mouhamadoul Toure, Emily Matter)
Major Tests: body composition by Bruker Biospec (in vivo) and carcass analysis; indirect calorimetry; food intake and body weight measurement; hypothalamic gene expression; cytokines; telemetry for activity, heart rate, blood pressure in unrestrained mice.

# 2008 Users: 8 (2 UC, 6 outside)
# 2008 Orders: 13
# 2008 tests: 357 (30 food intake, 75 indirect calorimetry, 252 body composition)

# 2007 Users: 10 (2 UC, 8 outside)
# 2007 Orders: 11
# 2007 tests: 232 (24 food intake, 80 indirect calorimetry, 128 body composition)

# 2006 Users: 11 (2 UC, 9 outside)
# 2006 Orders: 14
# 2006 tests: 2139 (93 food intake, 624 indirect calorimetry, 1422 body composition)

**A3. University of Cincinnati MMPC Database Statistics**

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
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</thead>
<tbody>
<tr>
<td>Snapshot</td>
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<tr>
<td># Completed Orders (database)</td>
<td>63</td>
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<tr>
<td>6/06-7/09 # Orders with payment:</td>
<td>20</td>
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<tr>
<td># Unique Investigators:</td>
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<td># Orders with data associated (database):</td>
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<td># Phenotype Assays (database):</td>
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<td># Assay Measurements (database):</td>
<td>39646</td>
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<td># Animals (database):</td>
<td>78</td>
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<td># Strains (database):</td>
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<tr>
<td># Publications (database):</td>
<td>49</td>
</tr>
</tbody>
</table>

**These numbers represent the data entered into the database, but in most cases do not accurately represent the workload of the Center. They serve as a measure of compliance with data entry guidelines.**

**B4. Tests Available at University of Cincinnati MMPC:**
Please see [http://www.mmpc.org/shared/catalog.aspx](http://www.mmpc.org/shared/catalog.aspx)

**B5. Progress in Technology at the University of Cincinnati MMPC**
Macrophage infiltration assay is being developed. Cytokine assays developed. Lymph fistula implemented in mice. Successful vertical sleeve gastrectomy and ileal transposition (bariatric surgery) in mice. Successful implementation of the pancreatic clamp at the UC MMPC. The Center is currently making labeled chylomicrons for metabolic studies and the isolated perfused liver is being set up for making labeled very low density lipoproteins for metabolic studies. New equipment purchased: P&Fs led to development of the non-invasive lipid absorption test.

**B6. Cincinnati MMPC Business Plan Survey**
See appendix F.

**B7. University of Cincinnati MMPC Spotlight on Careers**
Cincinnati MMPC routinely uses money from the dean’s fund and other sources to supplement the costs of tests to new PIs, especially those working to acquire preliminary data for their first research grant applications.

Promoting young investigators has been a major goal of the UC MMPC. Dr. Michele Battle, a young faculty that requested services from the UC MMPC, was greatly benefited by the center. Not only has the MMPC played a key collaborative role in Dr. Battle’s GATA4 research, but the Director of the MMPC, Dr. Tso, has also served as a reference and mentor for Dr. Battle in matters of research development and professional growth. In October, 2007, Dr. Tso wrote a formal letter of support for Dr. Battle’s K01 Mentored Research Scientist Development Award application in which he promoted Dr. Battle’s research and offered his services as a mentor on her advisory committee should she receive the grant for her project. In January, 2008, Dr. Tso also composed a letter of reference at Dr. Battle’s request in support of her application for a faculty position in the Department of Biological Sciences at Marquette University.

As a result of the MMPC’s enthusiasm to collaborate with a young investigator like Michele Battle, Dr. Battle has since referred two colleagues to the MMPC as well, including Dr. Karim SI-TAYEB, Ph.D., and Dr. D.J. Sidjanin, Ph.D. Both Dr. SY-TAYEB and Dr. Sidjanin are now currently collaborating with the MMPC on projects of their own.

Since her initial contact with the Cincinnati Mouse Metabolic Phenotyping Center (MMPC) in October, 2006, Dr. Michele Battle, Ph.D., an instructor in the Department of Cell Biology, Neurobiology and Anatomy at the Medical College of Wisconsin, has made several exciting contributions to the study of the role transcription factors in the development and function of the liver and intestines. Based, in large part, on data collected and analyzed in cooperation with the MMPC, Dr. Battle has found evidence which points to the criticality of GATA4 in the effective uptake of lipids and cholesterol in the intestine. Because of her achievements, she has been offered a position as an Assistant Professor of her Department at the Medical College of Wisconsin.

In addition, the UC MMPC provides training to investigators. These investigators are invited to the GRI for several days of training with our staff. During their week stay, investigators can observe our surgeon performing the lymph cannulation surgery, speak directly with the staff and directors, and attempt the surgery on their own. Several young investigators that have benefited from this training are Dr. Rene Commerford from Novartis, and Dr. Xiaosong Li from Albert Einstein College of Medicine.

Lastly, the UC MMPC has started a Seminar Series in which bi-monthly invited speakers visit the University of Cincinnati’s Genome Research Institute for two days. During this time, the invited faculty will meet with investigators at GRI and give a seminar relating to their research. Three Seminar Speakers have been listed below:

Dr. Gary Schwartz, Albert Einstein College of Medicine: “Distributed Nutrient Sensing in the Control of Energy Balance"
Dr. Alan Watts, University of Southern California: “The Beginning and the End of Anorexia: Insights from Thirsty Rats"

Dr. Streamson Chua, Columbia University: “Leptin Independent Regulation of Ingestion and Adiposity"

**B8. MMPC Directors’ Statement**

It has been both exciting and challenging in directing the Cincinnati MMPC. I have particularly enjoyed interacting with so many investigators on their projects. It is extremely fulfilling for me to work with young investigators by assisting with their research and suggesting experiments to strengthen their grant applications. With the support from the university and money generated through our services, we have been able to continue to advance by offering new services and purchase new equipment. The recent establishment of our seminar series has enabled center investigators to present their exciting work as well as inviting prominent investigators to present their work and critique the work of this center. I look forward to continue to work hard for the success of this center.

**B9. University of Cincinnati MMPC Research Highlights/published papers**

A new collaboration between the Cincinnati MMPC and an NIH Roadmap metabolomics laboratory headed by Herbert Hill at Washington State University led to the discovery of >3000 metabolites in rodent lymph.

Kimberly Kaplan, Prabha Dwivedi, Sean Davidson2, Qing Yang, Patrick Tso, William Siems1 and Herbert H. Hill Jr., Monitoring Dynamic Changes in Lymph Metabolome of Fasting and Fed Rats by Electrospray Ionization-Ion Mobility Mass Spectrometry (ESI-IMMS), Submitted to Analytical Chemistry.

Collaborating with the Yale MMPC Center has resulted in a Cell paper published last year.


43. McNamara RK, Able J, Jandacek R, Rider T, Tso P. Gender differences in rat erythrocyte and brain docosahexaenoic acid composition: Role of ovarian hormones
C. MMPC at UTSW
http://www4.utsouthwestern.edu/rogersnmr/mousepheno.htm

C1. Brief Center Description
The UTSW MMPC focuses on measuring intermediary flux rates in heart and liver using NMR, stable isotopes and positional isotopomer analysis. These tests yield information about TCA cycle rates in mitochondria, anaplerotic flux, glucose and glycogen kinetics, gluconeogenesis fluxes and fatty acid oxidation rates. In addition, they measure high energy phosphate metabolism. This Center has been in operation since 2000, but the first five years were focused on research and development of the tests, which are now standardized and offered on a fee for service basis. The tests are low throughput, require specialized NMR and MS instrumentation and expertise, and require considerable time for consultation, experimental design, data analysis and interpretation (in general tests require about a month to complete, and each core can have about three studies going on at any given time). Center personnel have focused on research and development, and have been instrumental in consortium efforts for database development, the funding programs, and developing/teaching MMPC courses.

Center Director: Dr. Craig Malloy
Co-Director: Dr. Shawn Burgess
Co-Director: Dr. Mark Jeffrey
Administrator: Marilyn English
Animal Core Director: Yue-Shoung Lu
Quarantine: X weeks
2009 Award: $350,000 direct costs
UTSW MMPC established July, 2000

C2. Self-Reported Data Statistics
The following numbers represent use of the cores reported in annual progress reports to the NIDDK

Program Income Reported:  Year -08  April, 2009:  $0
                           Year -07  April, 2008:  $0
                           Year -06  April, 2007  $0

Annual reports:
April, 2009:  4 papers, 5 conf abstracts (all UTSW)
April, 2008:  6 papers (all UTSW)
April, 2007:  5 papers (all UTSW)

*Tracking papers published with data provided from the MMPCs remains difficult as not all users remember to acknowledge the grants or the Centers. Papers listed as ‘UTSW’ have at least one author from UTSW MMPC but many are written by external MMPC users.

Intermediary Metabolism-NMR Core
https://www.mmmpc.org/secure/shared/showCenterCore.aspx?id=22
Core Directors: Craig Malloy, Shawn Burgess, Mark Jeffrey
Staff: 3.5 FTE (Angela Milde, Tian Teng He, Roshi Mehdibeigi, Scott Sabelhaus, Karolos Moreno)

Major Tests: Perfused organ and whole animal metabolism: isotopic measurements of glucose metabolism, TCA cycle, gluconeogenesis, triglyceride synthesis, high phosphate energy metabolism, urea cycle, ketone body metabolism.

# 2008 Users: 29 (14 UTSW)
# 2008 Orders: 29 (6 cardiac metabolism, 23 liver)
# 2008 animals: 477
#2008 tests: 1230 (see table below)

# 2007 Users: 15 (5 UTSW)
# 2007 Orders: 15
# 2007 animals: 216 (171 isolated tissues, 45 in vivo)
#2007 tests: 442

# 2006 Users: 15 (5 UTSW, 1 foreign))
# 2006 Orders: 15 (mostly liver fluxes)
# 2006 animals: 181 (145 isolated tissues, 36 in vivo)
#2006 tests: 380

**C3. UTSW MMPC Database Statistics**

<table>
<thead>
<tr>
<th>Tests</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1-9) Isotopomer analysis of extracts shipped to UT Southwestern</td>
<td>20</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>(10) Glucose production in isolated liver</td>
<td>50</td>
<td>94</td>
<td>215</td>
</tr>
<tr>
<td>(11) TCA flux in isolated liver</td>
<td>50</td>
<td>94</td>
<td>215</td>
</tr>
<tr>
<td>(12) Substrate oxidation in isolated liver</td>
<td>50</td>
<td>94</td>
<td>230</td>
</tr>
<tr>
<td>(14) Substrate oxidation in isolated heart</td>
<td>40</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>(15) TCA cycle flux in isolated heart</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>(16) Triglyceride synthesis in heart</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(17) Triglyceride synthesis in liver</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(18) High energy phosphates in isolated tissue</td>
<td>20</td>
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<tr>
<td>(19) Endogenous glucose production</td>
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<tr>
<td>(20) In vivo sources of plasma glucose</td>
<td>50</td>
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<td>120</td>
</tr>
<tr>
<td>(22) In vivo hepatic TCA cycle turnover</td>
<td>20</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>(26) Endogenous ketone turnover</td>
<td>-</td>
<td>10</td>
<td>120</td>
</tr>
<tr>
<td>(27) Endogenous urea turnover</td>
<td>-</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>(28) In vivo lipolysis by glycerol turnover</td>
<td>-</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>(29) Imaging studies</td>
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<td>30</td>
<td>50</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>380</strong></td>
<td><strong>442</strong></td>
<td><strong>1230</strong></td>
</tr>
</tbody>
</table>

# Pending Orders (database): 2
**These numbers represent the data entered into the database, but in most cases do not accurately represent the workload of the Center. They serve as a measure of compliance with data entry guidelines.**

C4. Tests Available at UTSW MMPC:
Please see [http://www.mmpc.org/shared/catalog.aspx](http://www.mmpc.org/shared/catalog.aspx)

C5. Progress in Technology at the UTSW MMPC
The MMPC provided the impetus to explore the use of NMR isotopomer analysis to measure metabolic flux in mice. The major challenge is the difficulty of acquiring high quality MR spectra in very small animals and samples. If spectra can be obtained, they tend to take a very long time to acquire. Spectra also take a lot of time and expertise to analyze and interpret. Two new MRIs installed for mouse imagine (9.4T, 7.0T), standardized mouse imaging protocols under development. Additional 600MHz spectrometer installed for analytical samples (2H MRS requires 8 hours/sample NMR time). LC/MS/MS system installed for isotope concentration/enrichment. Hepatic fat oxidation (LC/MS/MS, in vivo) method developed and published. Hyperpolarized 13C methods under development, focused currently on pyruvate metabolism in heart (highly novel research, high risk, high payoff). Mouse brain glucose metabolism positional isotopomer analysis methods under development. UTSW MMPC obtained ARC approval for mouse breeding to reduce problems with mouse transfer. The examination of substrate oxidation in the mouse heart has been standardized, to include an examination of only long chain fatty acid oxidation and glucose oxidation.

C6. UTSW MMPC Business Plan Survey
See appendix F.

C7. UTSW MMPC Spotlight on Careers
The MMPC program encourages participation of junior investigators in key Core positions. These junior scientists supply MMPCs with a superior source of expertise compared to standard technician staffing and benefits the junior investigator by providing salary support as well as exposure to a professional/scientific support network, both of which are crucial for the early development of an independent academic career. Dr. Burgess is an excellent example of how the MMPC nurtures careers of junior faculty and allows a natural and certain progression towards independence. Dr. Burgess started working with the UT Southwestern MMPC during his post-doctoral period 8 years ago. Two years later he was awarded a Junior Faculty grant from the ADA base on work started as an MMPC project. He has since progressed to a
tenure-track Assistant Professor with independent RO1 and ADA support, while continuing to serve in the UT Southwestern MMPC. One of the benefits to young MMPC faculty is the ability to work closely with very senior researchers from outside the parent institution. Dr. Burgess has benefited from his association with the MMPC, resulting in a number of successful productive relationships and impactful papers.

C9. UTSW MMPC Research Highlights


D. MMPC at Vanderbilt University
http://www.mc.vanderbilt.edu/mmpc

D1. Short Description
The Vanderbilt MMPC is a full service Center funded since 2000. It has three test cores focused on energy balance, and whole body metabolism where the predominant experiment is the insulin clamp; on cardiac and kidney function; and an analytical core to measure hormones, metabolites, etc. in plasma. The Vanderbilt personnel have been extremely active in the MMPC, and are especially involved in comparing and validating tests, establishing protocols, teaching and establishing MMPC policies and guidelines.

Center Director: David H. Wasserman
Associate Director: Alan D. Cherrington
Associate Director: Mark A. Magnuson
Assistant Director of Technology Transfer: Dr. Julio Ayala (left Vanderbilt 6/2009)
Administrator: Fran Tripp
Animal Core Director: Kenneth J. Salleng, DVM
Quarantine: 6-9 weeks
2009 Award: $570,948 direct costs
Vanderbilt MMPC established July, 2000

D2. Self-Reported Data Statistics
The following numbers represent use of the cores reported in annual progress reports to the NIDDK

Program Income Reported:  Year -08 April, 2009:  $371,726
Year -07 April, 2008:  $338,461
Year -06 April, 2007  $308,318
Total $1,018,505

Published Papers referencing DK059630*:  108 papers total (Pubmed, published between 6/1/2006 and 7/30/2009)
Annual reports April, 2009:  42 papers (30 Vanderbilt)
April, 2008:  23 papers (21 Vanderbilt MMPC)
April, 2007:  39 papers (31 Vanderbilt)
Total:  104

*Tracking papers published with data provided from the MMPCs remains difficult as not all users remember to acknowledge the grants or the Centers.

Metabolic Pathophysiology Core
Core Directors: Owen P. McGuinness
Associate Director: Masakazu Shiota
Energy Balance Subcore Director: Kate Ellacott
Tissue and In vivo Imaging Subcore Director: David Piston
Tissue and In vivo Imaging Subcore Associate Director: Sam Wells
Murine Pancreatic Islet isolation Subcore Director: Marcela Brissova
Staff: research associates (Carlo Malabanan, Tasneem Ansari, Emily Vest, Anastasia Golovin, Deanna Bracy)
Major Tests: carbohydrate metabolism including pancreatic clamps, glucose and insulin tolerance tests, vein, artery, cerebral ventricle cannulation, amino acid kinetics, indirect calorimetry, exercise, food consumption, body composition, real time cellular imaging, islet isolation and insulin secretion.
Costs for Services: calculated at 60% total Center cost for test for academic users.

# 2008 Users/Orders: 51 (36 Vanderbilt, 2 industry, 1 foreign)
# 2008 Tests: 10,200
Program income: $241,886

# 2007 Users: 62 (35 Vanderbilt, 3 industry, 2 foreign)
# 2007 Tests: 5092
Program income: $202,628

# 2006 Users: 35 (25 Vanderbilt)
# 2006 Tests: 3710
Program income: $197,649

Metabolic Pathophysiology Core Methods papers:
2. Glucose Metabolism in Vivo in Four Commonly Used Inbred Mouse Strains
3. Long Chain Fatty Acid Uptake *in Vivo*: Comparison of [125I]-BMIPP and [3H]-Bromopalmitate

**Cardiovascular Pathophysiology & Complications Core**
Core Director: Douglas E. Vaughan
Associate Core Director: Jeffrey Rottman
Staff: Michael Hill, Ph.D., ZhiZhang Wang, Lianli Ma, M.D.
Major tests: cardiac morphology, echocardiography, electrocardiography, telemetry, blood pressure, vascular morphology, heart rate variability, ventricular hemodynamics. Kidney perfusion, histopathology, GFR, albuminuria, renal blood flow, other renal function parameters that can be affected by diabetes and/or obesity.
Costs for Services: calculated at 60% total Center cost for test for academic users.

# 2008 Users: 29 (27 Vanderbilt)
# 2008 Tests: 2280
2008 Program income: $27,775

# 2007 Users: 34 (30 Vanderbilt)
# 2007 Tests: 2782
2007 Program income: $47,583
Cardiovascular Pathophysiology/Complications Core Methods papers:

1. Characterization of Susceptibility of Inbred Mouse Strains to Diabetic Nephropathy
2. Echocardiographic Evaluation of Ventricular Function in Mice
3. Temporal Changes in Ventricular Function Assessed Echocardiographically in Conscious and Anesthetized Mice

**Analytical Resources Core**
Core Director: Sergio Fazio
Associate Director: MacRae Linton
Hormone Assay Subcore Managing Director: Alan D. Cherrington
Hormone Assay Subcore Laboratory Manager: Wanda Snead
Lipids, Lipoproteins, Atherosclerosis Subcore Managing Director: Larry L. Swift
Immunohistochemistry Subcore Managing Director: Lillian B. Nanney
Staff: 1.1 FTE research assistants (Kathleen Smith, Mouhamadoul Toure, Emily Matter)
Major Tests: hormones, catecholamines, leptin, plasma and tissue lipids, phospholipids, lipoproteins, tissue microdissection and histopathology.
Costs for Services: calculated at 60% total Center cost for test for academic users.

# 2006 Users: 27 (23 Vanderbilt)
# 2006 Tests: 3853
2006 Program income: $22,419

# 2006 Cardiovascular Pathophysiology/Complications Core Methods papers:

1. Characterization of Susceptibility of Inbred Mouse Strains to Diabetic Nephropathy
2. Echocardiographic Evaluation of Ventricular Function in Mice
3. Temporal Changes in Ventricular Function Assessed Echocardiographically in Conscious and Anesthetized Mice

Analytical Resources Core
Core Director: Sergio Fazio
Associate Director: MacRae Linton
Hormone Assay Subcore Managing Director: Alan D. Cherrington
Hormone Assay Subcore Laboratory Manager: Wanda Snead
Lipids, Lipoproteins, Atherosclerosis Subcore Managing Director: Larry L. Swift
Immunohistochemistry Subcore Managing Director: Lillian B. Nanney
Staff: 1.1 FTE research assistants (Kathleen Smith, Mouhamadoul Toure, Emily Matter)
Major Tests: hormones, catecholamines, leptin, plasma and tissue lipids, phospholipids, lipoproteins, tissue microdissection and histopathology.
Costs for Services: calculated at 60% total Center cost for test for academic users.

# 2008 Users/Orders: 109 (64 Vanderbilt)
# 2008 Tests: 3847
2008 program income: $129,065

# 2007 Users/Orders: 116 (64 Vanderbilt)
# 2007 Tests: 2465
2007 program income: $88,250

# 2006 Users/Orders: 140 (79 Vanderbilt)
# 2006 Tests: 873
2006 program income: $88,250

D3. Vanderbilt MMPC Database Statistics**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
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<tr>
<td># Orders with payment:</td>
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<td># Unique Investigators:</td>
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<td># Orders with data associated (database):</td>
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<td># Assay Measurements (database):</td>
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<td># Animals (database):</td>
<td>33</td>
</tr>
<tr>
<td># Strains (database):</td>
<td>3</td>
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</table>
# Publications (database):

**These numbers represent the data entered into the database, but in most cases do not accurately represent the workload of the Center. They serve as a measure of compliance with data entry guidelines when compared to self-reported Center activity.**

## D4. Tests Available at Vanderbilt MMPC:
Please see [http://www.mmpc.org/shared/catalog.aspx](http://www.mmpc.org/shared/catalog.aspx)

## D5. Progress in Technology at the Vanderbilt MMPC

## D6. Vanderbilt MMPC Business Plan Survey
See appendix F.

## D7. Vanderbilt MMPC Spotlight on Careers
Career development has been an important focus of the MMPC. Three mechanisms have been used for this purpose.

a) Investigators seeking to acquire preliminary data for NIH grant applications or new investigators without secure funding bases are provided services at a reduced cost. This facilitates new research programs and serves as a sound investment mechanism as investigators served in this way have, in some cases, become major users that help support the MMPC.

b) Instructional resources (course, informal training, web-based information) are provided to investigators wishing to establish technology that will aid in the development of their own laboratories. This aids in the development of new laboratories wishing to have mouse metabolic phenotyping as a primary tool and it expands the impact of the MMPC by having the standardized practices developed by the MMPC implemented more broadly.

c) Incorporate new investigators into the operations of the MMPC. The MMPC has provided new investigators with experience, exposure, and opportunities that have been instrumental to their career development. Involvement with the MMPC has also given new investigators identifiable local and national service that have been important to promotions. Drs. Julio Ayala and Kate Ellacott joined the MMPC as non-tenure track faculty at the level of instructor. Dr. Ayala is now a tenure track Assistant Professor at the Burnham Institute in Orlando and Dr. Ellacott will be appointed to the tenure track at the level of Assistant Professor at Vanderbilt effective in September. Drs. Ayala and Ellacott have been invaluable to the operations of the MMPC, bringing expertise and a new perspective to phenotyping practices. Dr. Owen McGuinness is an established investigator with considerable expertise in the study of metabolism in large animal models. He has been Director of the Metabolic Pathophysiology Core since
2001. His involvement with the MMPC has diversified and expanded his own research program. At the same time, the knowledge that Dr. McGuinness brings to the MMPC in the study of metabolism in vivo has been of great importance in bringing sound in vivo experimental practices to the mouse.

These instruments for career development and growth are not only effective, but also sustainable. It is important to recognize that the MMPC career development practices have served the broader function of contributing either to MMPC growth, function, or research impact.

**D8. MMPC Directors’ Statement**

The mission of the MMPC, as set forth with the inception of the program, “is to advance medical and biological research by providing the scientific community with standardized, high quality metabolic and physiologic phenotyping services for mouse models of diabetes, diabetic complications, obesity and related disorders.” This remains the mission. The means by which this mission is achieved, however, has evolved based on the needs of the scientific community, logistical issues, and the obtainment of a sustainable business model.

The primary objective of the three experimental cores described above is to be a service provider. The services for the Metabolic Pathophysiology Core and Cardiovascular Pathophysiology and Complications Cores generally involve the transfer of mouse and assistance in design and interpretation of phenotyping tests. The Analytical Resources Core, which has developed assays for the small tissue mass and low blood volume of the mouse, has been important because it provides novel resources without the constraints and time cost of animal transfer. We found that the MMPC could be most responsive to the scientific community and broaden our scientific impact by making the procedures for Vanderbilt phenotyping tests, in particular those for glucose clamping which involve animal transfer, accessible to those anticipating regular use of those tests and wishing to learn them. This philosophy has allowed the standardized MMPC phenotyping procedures to be applied to a greater number of mouse models than would otherwise be possible. MMPC surgical and glucose clamp procedures are made available through our annual course “Glucose Clamping the Conscious Mouse”, by hosting investigators from other laboratories, by posting the detailed Vanderbilt laboratory manual on the web, and through journal-based publications.

The business model of the MMPC has been made sustainable by regular reviews of business practices, efficient use of skilled personnel, and by relationships with pharmaceutical and biotechnical companies which provide for center growth and other programs. With regard to the latter, the MMPC negotiates a “Resource Fee” which is 30 to 50% of the service cost. This added income allows the MMPC to assist new investigators, develop new technology, and contributes to laboratory maintenance and growth.

The cornerstones of the MMPC are services, education, standardization, and development. The MMPC is a valuable asset to the scientific community and has enriched the academic institutions that sponsor them. The Vanderbilt Diabetes Research and Training Center and the MMPC have a synergistic relationship, which has been important in strengthening cores, bringing in speakers, and facilitating the development of new investigators. The Vanderbilt
MMPC has enhanced my own research and given me, as Director, the opportunity to have a
greater impact on diabetes research.

**D9. Vanderbilt MMPC Research Highlights/published papers**

Ayala JE, Bracy DP, Hansotia T, Flock G, Seino Y, Wasserman DH, and Drucker DJ. Insulin
action in the double incretin receptor knockout mouse. Diabetes 57: 288-297, 2008. (MPC, ARC)

Ayala JE, Bracy DP, James FD, Julien BM, Wasserman DH, and Drucker DJ. The glucagon-
like peptide-1 receptor regulates endogenous glucose production and muscle glucose uptake

Berglund ED, Li CY, Poffenberger G, Ayala JE, Fueger PT, Willis SE, Jewell MM, Powers
AC, and Wasserman DH. Glucose metabolism in vivo in four commonly used inbred mouse

Coenen KR, Gruen ML, Lee-Young RS, Puglisi MJ, Wasserman DH, and Hasty AH. Impact
of macrophage toll-like receptor 4 deficiency on macrophage infiltration into adipose tissue
and the artery wall in mice. Diabetologia 52: 318-328, 2009. (MPC, ARC)

Neel BG, and Bence KK. Liver-Specific Deletion of Protein-Tyrosine Phosphatase IB
(PTP1B) Improves Metabolic Syndrome and Attenuates Diet-Induced Endoplasmic

Han BG, Hao CM, Tchekneva EE, Wang YY, Lee CA, Ebrahim B, Harris RC, Kern TS,
Wasserman DH, Breyer MD, and Qi Z. Markers of glycemic control in the mouse:
comparisons of 6-h- and overnight-fasted blood glucoses to Hb A1c. Am J Physiol Endocrinol

Kawamori D, Kurpad AJ, Hu J, Liew CW, Shih JL, Ford EL, Herrera PL, Polonsky KS,
McGuinness OP, and Kulkarni RN. Insulin signaling in alpha cells modulates glucagon

Rocheleau JV and Piston DW. Combining Microfluidics and Quantitative Fluorescence
Microscopy to Examine Pancreatic Islet Molecular Physiology Methods in Cell Biology. In:
Biophysical Tools for Biologists, Volume Two: In Vivo Techniques (Volume 89 ed.), edited
by Dr. John J. Correia and Dr. H. William Detrich I: Academic Press, 2008, p. 71-92. (MPC)

Shearer J, Coenen KR, Pencek RR, Swift LL, Wasserman DH, and Rottman JN. Long chain
fatty acid uptake in vivo: comparison of [125I]-BMIPP and [3H]-bromopalmitate. Lipids 43:
703-711, 2008.(MPC, ARC)


Brissova M, Powers AC. Revascularization of Transplanted Islets: Can It Be Improved? Diabetes 57: 2269, 2008 (MPC)


Gao, Z., Yin, J, Zhang, J., He, Q., McGuinness, O.P. and Ye, J. Inactivation of NF-KB p50 leads to insulin sensitization in liver through post translational inhibition of P70S6K. J. Bio. Chem (In Press) (MPC)


Ackermann Misfeldt, A., R.H. Costa, and M. Gannon, b-cell proliferation, but not neogenesis, following 60% partial pancreatectomy is impaired in the absence of Foxml. Diabetes 57, 3069-3077. (MPC, ARC)


Ayala JE, Bracy DP, Julien BM, Rottman JN, Fueger PT, Wasserman DH. Chronic treatment with sildenafil improves energy balance and insulin action in high fat-fed conscious mice. Diabetes. 2007 Apr;56(4):1025-33


Ayala JE, Bracy DP, Fueger PT, Wasserman DH. Chronic PDE5 inhibition increases energy expenditure, reduces fat mass and improves insulin action in high fat-fed conscious mice. Diabetes in press.


A. MMPC at University of Washington
http://www.mmpc.washington.edu/

A1. Brief Center Description
The Seattle MMPC was established in August of 2006. The strengths of this MMPC are energy balance, cardiac function and macrovascular complications, and kidney histopathology and microvascular complications. It is the primary MMPC focused on diabetic complications and is the main MMPC with which AMDCC collaborates. The Center has worked hard during the first three years to establish protocols and on research and development of new tests. Center staff have also been very active in consortium activities, particularly in establishing administrative guidelines, in funding programs, and in collaborative research projects.

Center Director: Dr. Renee C. LeBoeuf
Co-Director: Dr. Michael W. Schwartz
Administrator: Donna Geronimo
Animal Core Director: Dr. Lillian Maggio-Price
Quarantine: 0-8 weeks. In some cases, with use of Flex Air units there is no quarantine time as we are able to work on mice immediately because the units are self contained and serve as the quarantine.
2009 Award: $551,055 direct costs
Seattle MMPC established August 2006

A2. Self-Reported Data Statistics
The following numbers represent use of the cores reported in annual progress reports to the NIDDK

Program Income (actual amount at the end of the budget year-after progress report was submitted):

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<thead>
<tr>
<th>Year</th>
<th>Income</th>
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<tr>
<td>Year 3 (6/1/08-5/31/09)</td>
<td>$103,918</td>
</tr>
<tr>
<td>Year 2 (6/1/07-5/31/08)</td>
<td>$98,457</td>
</tr>
<tr>
<td>Year 1 (8/24/06-5/31/07)</td>
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Published Papers referencing DK076126*: 4 papers total (Pubmed)

<table>
<thead>
<tr>
<th>Annual reports</th>
<th>2009: 12 papers (11 Seattle MMPC)</th>
</tr>
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<tr>
<td>April, 2008</td>
<td>--</td>
</tr>
<tr>
<td>April, 2007</td>
<td>--</td>
</tr>
<tr>
<td>Total:</td>
<td>12</td>
</tr>
</tbody>
</table>

*Tracking papers published with data provided from the MMPCs remains difficult as not all users remember to acknowledge the grants or the Centers.

# 2008 Users: 27 (12 UW) – overall, 42 users at the MMPC (57% UW)
# 2008 Orders: 70 (32 UW)
# 2007 Users: 19 (11 UW)
# 2007 Orders: 36 (28 UW)

# 2006 Users: 10 (8 UW)
# 2006 Orders: 10 (8 UW)

# letters of support for grant applications: >12

**Diabetes and Energy Balance Core/Analytical HUB/Metabolic HUB**
Core Director: Michael Schwartz
Co-Director: Gregory Morton
Associate Core Director: Mark Wener
Staff: Kayoko Ogimoto, Jonathan German, Timothy McMillen, Mark Caldwell, Iaela David
Major Tests: The Diabetes and Energy Balance Core offers body comp, body temp, energy expenditure and meal pattern analysis. The Analytical HUB offers hormone assays, cytokines, lipoprotein/cholesterol, other metabolites including lipids, hepatic and kidney function. The Metabolic HUB offers glucose tolerance and insulin sensitivity measures, carcass analysis, hypothalamic gene expression.

# 2008 Animals: 280: 181 body composition, 45 body temp, 79 energy expenditure, 45 meal pattern analysis, 20 glucose tolerance, 8 insulin sensitivity
# 2008 Samples: 438 (analytical HUB)

# 2007 Animals: 543: 253 body composition, 38 body temp, 100 energy expenditure, 40 meal pattern analysis, 70 glucose tolerance, 70 insulin sensitivity
# 2007 Samples: 106 (analytical HUB)

# 2006 Animals: 72: 72 body composition
# 2006 Samples: --

**Cardiovascular Core**
Core Director: Charles Murry
Co-Director: Elina Minami
Staff: Jennifer Deem
Major tests: Specializes in heart rate, blood pressure, blood flow, cardiac function, echocardiography/electrocardiography, left ventricular catheterization, arterial response to injury, myocardial infarction. Measurements are made in the intact animal or isolated heart.

#2008 Users: 4 new
#2008 Animals: 94: 57 echocardiography, 10 invasive hemodynamics, 23 open thoracotomy, 9 drug injection

# 2007 Users: 2
# 2007 Animals: 14: 6 invasive hemodynamics, 8 bone marrow transplantation
# 2006 Users: --
#2006 Animals: --

**Nephrology, Macrovascular and Microvascular Core**
Core Director: Charles Alpers
Co-Director: Kevin O’Brien
Staff: Kelly Hudkins-Loya, Tomasz Wietecha, Thomas McDonald, Jinkyu Kim, Mariko Koelling

# 2008 Samples: 713
# 2007 Samples: 539
# 2006 Users: 10
# 2006 Samples: 118

**A3. Washington MMPC Database Statistics**

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<th>Category</th>
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<td># Assay Measurements (database)</td>
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<td># Animals (database)</td>
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<td># Strains (database)</td>
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<tr>
<td># Publications (database)</td>
<td>3</td>
</tr>
</tbody>
</table>

**These numbers represent the data entered into the database, but in most cases do not accurately represent the workload of the Center. They serve as a measure of compliance with data entry guidelines.**

**A4. Tests Available at Seattle MMPC:**
Please see [http://www.mmpc.org/shared/catalog.aspx](http://www.mmpc.org/shared/catalog.aspx)

**A5. Progress in Technology at the Seattle MMPC:**
Developing the insulin clamp—working on rats, may move to mice. Improving equipment and processes for energy balance/ indirect calorimetry measurements. The Seattle MMPC is exploring the use of portable Flex-Air units to transport animals between facilities without a quarantine period, and this has worked well so far. It allows for ‘one stop shopping’—the ability for a single set of mice to be studied in several cores, since they can be housed ‘on the road’ and don’t have to be immediately sacrificed once they leave the animal facility. The MMPC struggles with obtaining sufficient equipment and personnel to efficiently run some of the cores, most notably the energy balance core. The original award didn’t allow for the
purchase of much equipment, and although the MMPC received a supplement of some of this needed equipment, the core still needed to apply for funds from NCRR for this infrastructure. This has been obtained, but funds are still low for the personnel needed to run it. This struggle for money for equipment has been an ongoing problem at several of the MMPCs. The Seattle MMPC is planning to introduce a new Hub into the Cardiovascular Core; Vascular Reactivity HUB. The central service provided by the proposed Vascular Reactivity Hub will be the measurement of contractile and dilatory signaling (or vasomotor function) of isolated blood vessels (ex vivo) from mice and encompasses both conduit and sinusoidal vascularized tissues. The estimated diameter of conduit vessels able to be studied ranges from 100-1000 \( \mu m \) with segments being \( \sim 2-3 \text{mm} \) in length for conduit rings and \( \sim 4-5 \text{mm} \) in length for tissue strips. In future months, we hope to also provide our service for smaller order "resistance" vessels using a pressure-dependent system.

A6. Seattle MMPC Business Plan Survey
See appendix F.

A8. AMDCC
An AMDCC researcher, Eva Feldman, is an investigator who sends mouse plasma samples to the MMPC routinely for profiling mouse plasma lipoproteins. Following Fast Performance Liquid Chromatography separation of lipoprotein fractions, the Center performs total cholesterol and triglyceride analyses.

Our Nephrology, Macrovascular, and Microvascular Core serves a primary function in assessing tissue pathology for all mice developed by the Jackson Laboratories for AMDCC Investigators.

A9. Directors’ Statement
Our original goals were to provide investigators with high quality phenotyping of mice for features of diabetic complications including atherosclerosis, kidney disease, and retinopathy, and to carefully and precisely evaluate each mouse for measures of energy balance and extent of obesity and diabetes. The Seattle MMPC is meeting these goals due to the enthusiastic and solid support of the Core Directors. We are fortunate that the Core Director’s and their personnel provide a broad expertise in the fields of ‘diabesity’ and diabetic complications. In most cases, core protocols were already in place prior to the initiation of our MMPC.

Perhaps the most difficult part of our MMPC development was instituting consistent billing, defining each protocol in a manner accessible to investigators’ ordering needs, and teaching investigators how to utilize the phenotypic measures.

One major feature of working with investigators is the time Core Directors spend to learn about investigator projects in order to guide investigators toward appropriate protocols and the time it takes Core Directors and their staff for data analyses and dissemination of this information to investigators. These are activities which are not directly charged but end up being one of the most important features of MMPC activities.
Overall, we are delighted to be part of the national MMPC consortium in part because of new collaborations we have made with investigators, opportunities to teach investigators at all stages of their career new aspects of using the mouse system, and interactions with other members of the MMPC consortium.

A10. Seattle MMPC Research Highlights
The following study demonstrates 'one-stop' shopping at Seattle MMPC. Dr. Yansong Gu created a strain of SirTI conditional knockout mice. SirTI acts as a nutrient sensor and modulates many transcription factors (e.g. Foxol, PPARg, PCG-la) that are implicated in adipogenesis and metabolism. He also generated an adipocyte-specific SirTI mouse model using aP2-cre transgenic mice and found that these mice are resistant to diet-induced obesity. His goal was to conduct a comprehensive metabolic profiling on these latter mice. Work was performed in four MMPC Cores/Hubs. The Energy Balance group obtained calorimetry, meal pattern analysis, and body temperature data. The Metabolic Hub accessed insulin resistance (IPGTT) and the Analytic Hub quantified insulin and glucose levels. The Microvascular Core processed kidney tissue from these mice which included paraffin embedding and histological staining. We found that male mutants are more insulin resistant than wild-types. Overall, this investigator was able to nearly completely characterize his new mouse strain using the Seattle MMPC.

In a study for the atherosclerosis group at Boehringer Ingelheim (Ridgefield, CT), we showed an increased atherosclerosis prevalent throughout the aorta in apoE-/- mice treated with specific drugs. This data was generated using our newest atherosclerosis morphology approach using coronal sections which generate 'candy cane' appearing sections of total aorta. We standardized this procedure in a separate pilot study of apoE-/- mice to show relationships between older en face approaches and the new coronal sectioning procedure.


subsets regulating glucose metabolism and energy homeostasis. Endocrinology, 2009 Feb;150(2):707-12. PMID: 18845632


F. MMPC at Yale University
http://www.mc.Yale.edu/mmpc

F1. Brief Center Description
The Yale MMPC focuses on in vivo metabolism with emphasis on the insulin clamp, energy balance, eating behavior and body composition, on pancreatic islet function, and on analysis of hormones, cytokines and metabolites, both unlabeled and those labeled with stable isotopes. It has been in existence since July 2000, and has provided tests for hundreds of investigators. Center staff have been very active in consortium activities, and have been particularly instrumental in developing the database, the funding programs, and developing and teaching MMPC courses.

Center Director: Dr. Gerald Shulman
Associate Director: Gary Cline
Administrator: Ann DeCosta/Debra Mento
Animal Core Director: James Macy, DVM
Quarantine: X weeks
2009 Award: $346,930 direct costs, awarded as subcontract to the CBU
Yale MMPC established July, 2000

F2. Self-Reported Data Statistics
The following numbers represent use of the cores reported in annual progress reports to the NIDDK

Program Income Reported:

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<th>Year</th>
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<tr>
<td>Year-08</td>
<td>$41,195 (Metabolomics Core).</td>
<td>$21,766 (Metabolomics Core).</td>
<td>$31,763 (Metabolomics Core).</td>
</tr>
<tr>
<td>Year-07</td>
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<td>$0 (Integrative Phys Core)</td>
<td>$0 (Integrative Phys Core)</td>
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Papers from DK076169/DK59635*: up to 46 papers, (6/06 – 7/09 Pubmed)

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<th>April, 2008</th>
<th>April, 2007</th>
<th>Total</th>
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<tr>
<td>Annual reports</td>
<td>27 papers (24 Yale)</td>
<td>15 papers (15 Yale)</td>
<td>16 (7 Yale)</td>
<td>58</td>
</tr>
</tbody>
</table>

*Tracking papers published with data provided from the MMPCs remains difficult as not all users remember to acknowledge the grants or the Centers. DK59635 funded the Yale MMPC from July 2000–June 2005, and DK76169 currently funds the Yale, Case, UTSW and CBU (MCG) MMPCs. Papers listed as ‘Yale’ have at least one author from Yale MMPC but many are written by external MMPC users.

Integrative Physiology Core
https://www.mmpc.org/secure/shared/showCenterCore.aspx?id=15
Core Directors: Varman Samuel
Staff: post doctoral fellows (Michael Jurzak, Francois Jornayvaz)
Major Tests: carbohydrate metabolism including pancreatic clamps, vein, artery, cerebral ventricle cannulation, indirect calorimetry, exercise, food consumption, body composition, islet isolation and insulin secretion, isolated hepatocyte characterization.

# 2008 Users: 28 (16 Yale, 12 outside institutions)
# 2008 Orders: 50

# 2007 Users: 21 (12 Yale, 9 outside)
# 2007 Orders: 33
#2007 Mouse Models: 21

# 2006 Users: 13 (3 Yale, 10 outside)
# 2006 Orders: 23
# 2006 Mouse models: 25
# 2006 tests: 7320 total: 1220 clamps, 30 cardiac action, 800 metabolic cage, 1600 body comp, 1100 tracer assays, 700 glucose uptake, 350 glycogen synthesis, 400 TG, 1100 FFA

Metabolomics Core
https://www.mmpc.org/secure/shared/showCenterCore.aspx?id=19
Core Director: Gary Cline
Staff: Rebecca Pongratz, Mario Kahn, Todd May

# 2008 Users: 33 (20 YALE, 13 outside institutions)
#2008 orders: 41
# 2008 Models: 17
Tests conducted: 15,890

# 2007 Users: 34 (20 Yale, 14 outside institutions)
#2007 Orders: 41
Tests conducted: 17,720

# 2006 Users: 23 (11 Yale, 12 outside institutions)
# 2006 Orders: 29
#2006 Tests conducted: 12,773

F3. Yale MMPC Database Statistics**

<p>| | | |</p>
<table>
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<tr>
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<td>Snapshot 6/06-7/09</td>
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<td># Orders from Yale</td>
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</tr>
<tr>
<td></td>
<td># Orders with payment:</td>
<td>0</td>
</tr>
</tbody>
</table>
# Unique Investigators: 21
# Orders with data associated (database): 41
# Phenotype Assays (database): 47
# Assay Measurements (database): 89,206
# Animals (database): 1146
# Strains (database): 10
# Publications (database): 60

**These numbers represent the data entered into the database, but in most cases do not accurately represent the workload of the Center. They serve as a measure of compliance with data entry guidelines.**

F4. Tests Available at Yale MMPC:
Please see [http://www.mmpc.org/shared/catalog.aspx](http://www.mmpc.org/shared/catalog.aspx)

F5. Progress in Technology at the Yale MMPC
Developed hypoglycemic clamp, in vivo fat oxidation in whole body and muscle. Developed LC/MS/MS assay of nucleotides/redox state (ATP, ADP, AMP, GTP, GDP, GMP, NADH, NADPH). Developed assays for Krebs cycle intermediates. Developed deuterium NMR method for analysis of deuterated glucose isotopomers (for gluconeogenic fluxes), LC/MS/MS method development to determine the mass isotopomer distribution of mitochondrial Kreb’s cycle intermediates and products of mitochondrial anaplerosis is on-line and has made a direct contribution to 5 publications. Islet perfusion apparatus that allows simultaneous perfusion of 8 islet preps (20 to 100 islets per prep) is on-line. Developing MRS assay for TCA flux in vivo. Integrative Physiology Core moved to renovated space in 2009 (larger, dedicated surgery area, space to expand CLAMS system to 16 cages).

F6. Yale MMPC Business Plan Survey
See appendix F.

F7. Yale MMPC Spotlight on Careers
Participating in the MMPC has directly benefited the careers of several young faculty members at Yale. In particular participating in the MMPC has: 1) provided national and international visibility for each of the Yale MMPC core directors, 2) allowed them to participate at the national level as a member of Executive Committee with their colleagues at each of the other MMPC member institutions, and 3) provided them with a unique opportunity to make highly significant scientific contributions studying the most current and relevant mouse models of diabetes and metabolic diseases. The success of the following Yale MMPC core directors and staff is due in large measure to their association with this program. Providing quality phenotyping of mouse models of metabolic diseases is highly demanding and technically difficult. Recognizing this, two of the past directors of the in vivo core of the Yale MMPC have been recruited to establish mouse metabolic phenotyping centers at other institutions. Jason Kim, Ph.D. was recruited to the University of Pennsylvania as an Associate Professor, and subsequently to the University of Massachusetts as Professor of Molecular Medicine to establish mouse metabolic phenotyping centers at these institutions. And, Cheo-Soo Choi, M.D., Ph.D. was recruited in 2008 by the Lee Gil Ya Cancer and Diabetes Institute
at Gachon University (Incheon City, Korea) as an Associate Professor to become the director of the first Korean Mouse Metabolic Phenotyping Center. Varman Samuel, M.D., Ph.D. now holds the position as director of the Yale MMPC in vivo core, where he has quickly established high visibility for his expertise and knowledge of metabolic diseases and is now an Assistant Professor. The services provided by the Metabolomics core with Gary Cline, Ph.D. has been recognized and valued by the Yale Medical School and this association has been instrumental in his promotion to Associate Professor.

F8. Directors’ Statement
The Yale Mouse Metabolic Phenotyping Center (MMPC) was established in 2000 as one of four cooperating MMPCs (Yale, University of Cincinnati, Vanderbilt University and University of Texas, Southwestern), expanded in 2005 to include two other centers (Case Western Reserve University and University of Washington, Seattle). The Yale MMPC consists of an Administrative Core and an Animal Core to support its two Phenotyping Cores (In Vivo Physiology Core and the Metabolomics Core). A first priority of the Yale MMPC was to streamline procedures to minimize quarantine of mice arriving from other investigators. Working closely with Dr. James Macy and the Yale Animal Resources Center, we have established quarantine space dedicated solely to the Yale MMPC, which gives us the capability to perform many of the phenotyping tests, such as body composition, activity and energy expenditure, while the mice are still in quarantine. To further optimize the process, we have established procedure rooms for surgeries and clamp studies dedicated to the MMPC, allowing us to perform all standard phenotyping tests of live mice within 3-4 weeks of arrival in our facilities. The Yale integrative physiology core conducts in vivo experiments and analytical assays to characterize metabolic phenotype of transgenic/knock-out mouse models potentially useful for understanding diabetes, its complications, obesity and related metabolic diseases or conditions. The Integrative Physiology continues to be highly sought-after resource and has consistently performed detailed metabolic phenotyping of over 1,000 genetically altered mice, representing more than 25 unique mouse models, each and every year since 2000. The Metabolomics Core strength in the use of tandem mass spectrometric analysis of lipid profiles, and the application of stable isotopes to metabolic flux analyses complements the work of the Integrative Physiology Core by opening a window into the mechanism underlying the observed phenotype. In conclusion, the Yale MMPC has established itself as a valuable resource to the scientific community by the dedication of its staff to quality research and innovation, and its commitment to the study of mouse models that will further our insight into the causes of the metabolic diseases of insulin resistance, obesity, and diabetes.

F9. Yale MMPC Research Highlights/Published Papers
The Yale MMPC has maintained a highly productive portfolio of manuscripts. This is in large part driven by our expertise in assessing insulin action in vivo with the hyperinsulinemic-euglycemic clamp but also the relatively high volume utilization of these services by collaborating investigators. The research can be categorized in broad themes. First, several studies have demonstrated the role of tissue specific fat accumulation as the critical event in the pathogenesis of insulin resistance. For example, Choi et al. (JCI 2007) demonstrated that overexpression of the mitochondrial uncoupling protein 3, prevented
against diacylglycerol accumulation and subsequent insulin resistance and Wang et al. (*Diabetes* 2009) demonstrated the role of LPL in the portioning of lipids into muscle, which without leads to compensatory lipid accumulation in other tissues with insulin resistance. Several papers (Vianna et al. *Cell Metab* 2006, Handschin et al. *JCI* 2007, and Choi et al. *PNAS* 2008) furthered our understanding of the biology of PGC1α as a regulator of mitochondrial biogenesis and the subsequent impact on muscle oxidative capacity. Additionally, several studies (Villena et al. *Diabetes* 2008, Ahmadian et al. *Diabetes* 2009, and Jaworski et al. *Nat Med*, 2009) contributed to our emerging understanding of the adiposome as a novel organelle of intracellular lipid storage. Finally, the Yale MMPC contributed significantly to manuscripts that probe the neural mechanisms of appetite regulation and glucose homeostasis (Gao et al. *Nat Med* 2007, Chen et al. *PNAS* 2006, Tong et al. *Cell Metab* 2007, Gillum et al. *Cell* 2008). The Yale MMPC continues to be approached by leading investigators for new collaborations in exciting areas of adipogenesis, inflammation and insulin signaling. In large part, these investigators seek us out based on our past successful performance but also with the express confidence that the studies performed by the Yale MMPC will significantly enhance a specific project and that the provide insights leading to high-impact publications.


G. I. "Suppression of diaclylglycerol acyltransferase-2 (DGAT2), but not DGAT1, with antisense oligonucleotides reverses diet-induced hepatic steatosis and insulin resistance" J Biol Chem 282(31), 22678-22688 2007


20. Rowe, G. C., Choi, C. S., Neff, L., Horne, W. C., Shulman, G. I., and Baron, R. "Increased energy expenditure and insulin sensitivity in the high bone mass DeltaFosB transgenic mice"Endocrinology 150(1), 135-143 2009


G. CBU at Medical College of Georgia
http://www.mmpc.org

G1. Short Description of the CBU
The Coordinating and Bioinformatics Unit was established in July 2005 and is shared by the national Mouse Metabolic Phenotyping Centers (MMPC) and Animal Models of Diabetic Complications Consortium (AMDCC). The CBU is charged with the development, housing and maintenance of the websites and databases, carries out administrative tasks, and organizes both separate and joint meetings for these consortia. It distributes funds and provides financial management for the MMPC and AMDCC Pilot and Feasibility programs and the MMPC MICROMouse funding program. This section will briefly describe the progress of the CBU to provide web- and database tools.

Center Director: Dr. Richard McIndoe
Co-PI for Biostatistics: Robert Podolsky
Database: Shan Bai
Computer Programmer: Stephen Whitfield
Web Programmers: Michael Aufiero and Vishal Doshi
Coordinator: Joann Higdon
CBU established: July, 2005
2009 Award: $ 3,395,277 total costs
   The award includes funds for three MMPC which are paid as subcontracts, and for three peer reviewed funding programs as well as funds for administering the two consortia, organizing meetings, and for building, upgrading, running and maintaining websites and databases.

G2. Consortium Administration
Meetings: The CBU organizes or supplies organizational and financial support for all meetings of the MMPC, including the monthly steering committee meetings, the annual meeting that takes place at one of the MMPCs each year, and subcommittee meetings. The CBU has designed web-based tools to facilitate the meetings and store minutes and other documents: https://www.mmpc.org/shared/meetings.aspx

Committees: https://www.mmpc.org/shared/committees.aspx this site allows the MMPC to keep track of committee members and their contact information as well as meeting minutes.

Funding programs: The CBU provides organizational support for all activities surrounding the funding programs. The CBU has also developed management software for the funding programs sponsored by the AMDCC and MMPC. This software is used to manage the review process and post-award activities. This includes communication with reviewers, applicants, and the secondary review groups. The system largely automates all the administrative processes, including automated emails to remind reviewers of critique deadlines and awardees of progress report deadlines. It maintains a record of all elements of the application and review process and stores them in an easily negotiated password-protected area of the website. The CBU also communicates with the applicant institutions, negotiates subcontracts
and transfers funds, and receives and tracks progress reports. Tools include training
documents for both applicants and reviewers.

Subcontracts: Three of the MMPC test Centers are funded as subcontracts through the CBU.
There was a second competition held in 2006 through the CBU for these awards, and the CBU
organized and facilitated this competition and the peer-review. Selection for funding was
based on priority score and was made by the NIH staff and the MMPC advisory committee.
This second competition was held in order to fill scientific ‘holes’ left after the NIH funded
three Centers through RFA DK05-008, that were identified by the MMPC advisors, including
the needs for additional capacity for insulin clamping, energy balance measurements, and
metabolic pathway flux measurements. The CBU established and maintains these
subcontracts, including collection of the progress reports and invoices. The CBU also funds
all P&F and MICROMouse research awards as subcontracts.

Membership: The CBU tracks all members of the MMPC in a password protected area: center
personnel, advisors, clients, students, P&F recipients, peer reviewers, etc. The CBU also
provides the security context for the membership of the MMPC. A role based security model
was developed to allow granularity with respect to secure activities on the web portal. For
example, individual Center administrators/personnel can only see orders and data from their
center. At this point membership stands at 745 MMPC members from 181 Institutions.

Orders: the CBU provides web tools to electronically submit orders, summarize and track
orders and other business practices at the MMPCs. These include an online test catalogue, an
online test order module, and an administrative section of the database in which orders,
animal data and client data is entered.

Training: The CBU has taken on the charge for training MMPC personnel and clients to use
various website tools, administrative tools, and to populate and use the database. They have
written web-based and static documents that walk Center staff and clients through some of the
more complex tools, and these are available at a password protected site

Website and Database: The CBU designed and built the MMPC and AMDCC websites
(www.mmpc.org and www.amdcc.org) and the shared database, along with a myriad of
electronic tools for administration, communication, data storage and query.

G3. Website www.mmpc.org
Test Catalog: https://www.mmpc.org/shared/catalog.aspx
This is the central focus of the MMPC website. It is a searchable catalog of all tests that can
be organized by Center site, Center core, category or keyword. Each entry contains a
description of the test. A user can also download a PDF document of the entire catalog that is
assembled on the fly and is current at any given point in time. Protocols can also be searched

New web tools (web services) provide individual MMPC centers a mechanism to
electronically retrieve the catalog data for their Center and display it on their center web sites.
This allows the centers to maintain their catalog information on the National MMPC site, but still have it displayed using their custom center site’s look and feel. This will allow both the National and individual MMPC sites to remain in sync with respect to their catalog information. In addition to the catalog, the MMPC web service created by the CBU also provides tools to retrieve data generated by the MMPC clients that has been released to the public by other websites. These tools provide the ability for other NIDDK resources to cross deliver data from the MMPC.

**Application for Services:** [https://www.mmpc.org/secure/order.aspx](https://www.mmpc.org/secure/order.aspx)

This is a secure password protected area that allows clients to order tests from any MMPC core online. A separate site allows Center personnel to search through orders using a variety of parameters. The web tools very nicely facilitate and enable the administration of orders.

**Centers Cores:** [https://www.mmpc.org/shared/cores.aspx](https://www.mmpc.org/shared/cores.aspx) This site contains descriptions and contact information, as well as test lists and descriptions, as a one stop shop to get a fast overview of the entire program.

**MMPC Publications:** the website contains a section that automatically tracks and records publications that reference the MMPC grant awards from the PubMed database, or that have been submitted from MMPCs. There are currently 337 publications in the system. [https://www.mmpc.org/shared/publications.aspx](https://www.mmpc.org/shared/publications.aspx)

**MMPC Client Institution Map:** [https://www.mmpc.org/shared/institutions.aspx](https://www.mmpc.org/shared/institutions.aspx) This section provides a Google map of the locations and identities of the client institutions that have completed orders using the MMPCs and the MMPCs themselves. The map “pins” are color coded to reflect the number of orders coming from that institution (see below).
Courses: The CBU established web pages to provide information regarding the MMPC courses, including an interactive downloadable agenda with course materials for the Isotope Course 
http://www.mmpc.org/shared/tracersAgenda.aspx. This allowed faculty to distribute course materials entirely electronically, and work on their materials until just before the lectures. See course pages at http://www.mmpc.org/shared/courses.aspx.

Presentations: 
https://www.mmpc.org/shared/presentations.aspx
This section contains presentations and posters presented by the MMPC personnel that are considered to be of interest.

Center Interface and Data Entry: The CBU built an interface for Center personnel to enter administrative data and test data into the database. The test data banking needs a flexible interface since the test data comes in many forms including time courses, spectra, computer outputs, histology images, etc; the analysis often results in data that is in a completely different form than that of the raw data; the experiments are somewhat standardized but the Cores often need to add in independent variables; the outcome of some tests are purely descriptive, etc. This environment creates a lot of challenges for a database. The MMPC/AMDCC database is modeled after the JAX Mouse Phenome 
http://phenome.jax.org/pub-cgi/phenome/mpdcgi?rtn=docs/home. For each experiment, the core staff starts with the order #, creates an experiment name, adds the animal strain, sex and age data, the catalog test number, phenotype assays, and when appropriate, other experimental conditions (metadata dependent on the test, such as insulin dose or mouse diet). These parameters are as standardized as possible, but the Center staff can add parameters to a category. The data is uploaded using a standardized data template spreadsheet created dynamically for each experiment which is downloaded directly from the database page devoted to that experiment. The data is then electronically curated and evaluated during the upload process before saving it to the database. Batch uploading of the data is imperative for because some tests have hundreds, if not thousands of associated data points.

Public Interface and Data Search: The data can be searched by a set few parameters at this point. One can search by ‘animal’, ‘assays’, ‘histology’, ‘strain’, or ‘experiment’, where the ‘experiment’ is a unique identifier. One can also search for papers, orders, and protocols. At this point as the database becomes populated, the most useful way to search for data is by ‘experiment’ (123 experiments have data entered so far although not all have been released to the public) http://www.mmpc.org/shared/experiments.aspx. One can also search by strain, for instance C57BL/6J has 44 experiments associated with it. When an experiment is selected, the page associated with it has all associated metadata, and the test data can be
downloaded by selecting ‘phenotype measurements’, and then the specific desired data points can be downloaded.

Data Analysis: https://www.mmpc.org/shared/analysisPhenotype.aspx Tools are provided that help database users assemble datasets from the banked phenotyping data and analyze them, including statistical analysis and graphical analysis.

Data Curation An important aspect of the MMPC web portal are the strategies to curate the data imported into the system. Data curation takes several forms and we use both algorithmic and structured data entry schemes to minimize errors. The most common data entry errors are due to the use of free text fields. These fields require the user to type information into the system. This can be prone to misspellings and the addition of unwanted characters (e.g. spaces). These errors make querying these fields difficult, because the query must take into account these variations. To avoid these errors, we use controlled vocabularies and ontologies whenever possible as drop down options during data entry or query. Another source of error can come while uploading the data to the system. To facilitate the data upload procedure and avoid these errors, we developed a common method and format for uploading phenotype assay data. Each experiment in the system has a data upload template that can be dynamically generated from the website. The MMPC staff can download this dynamically generated Excel template, cut-and-paste their results in the template and upload the Excel file to the website. Once uploaded, the data is validated and any validation errors corrected prior to saving it to the database. For validation, we developed a very simple curation mechanism that flags potentially incorrect data and requires the users to correct it before saving the data to the database. Numerical, categorical and date/time fields are all evaluated during this process. All assays in the system have units of measure and valid data ranges attached to them. We use these ranges during the upload process to validate the data before saving it to the system. During this process, the animal information is also uploaded and curated for valid birth and death dates and sex determination.

Future plans:
- Develop better data exploration and statistics tools to serve investigator needs
- Develop microarray analysis/visualization tools
- Continue work on controlled vocabularies for histology and enhanced analytical tools
- Work with the UTSW group to incorporate MRI data in the MMPC web portal.

G5. CBU MMPC Research Progress


G6. Directors’ Statement

In addition to providing both the administrative and bioinformatics infrastructure for the MMPC, the CBU also provides one-on-one consultations and interactions with both the MMPC Center staff and administrators and the AMDCC Pathobiology site personnel. These activities take the form of either a teleconference or web conference to discuss issues or provide advice. The web conferences are particularly helpful as it provides a visual aid when discussing potential issues or during training sessions. The CBU uses GoToMeeting (www.gotomeeting.com) for this function. A nice feature of this software is it allows the CBU to see the desktop of others in the meeting during the web conference as many times it is helpful to see what the users see to troubleshoot and train.

Stability of the MMPC/AMDCC web portals is paramount and the CBU has also designed an error subsystem to track and notify the CBU when website errors occur. Normally, our software design traps and handles potential website errors and displays these issues to the user in a graceful and controlled manner (rather than abruptly dumping the users to the default IIS error page). However, there are times when a website error occurs that was not trapped. As not everyone will notify us of the error, we created a subsystem that will generate an email that provides the CBU with the contact information of the user that encountered the error (if they are logged in), the page the error occurred, the history of the pages they visited and the stack trace for the error. With this information we can track down the error and fix the problem.

The philosophy of the CBU is to take a proactive view of its responsibilities to manage and organize the activities of both the MMPC and AMDCC. All the personnel in the CBU, including the programmers, are expected to be available to the membership for questions, concerns or help. For example, during the MMPC Isotope Tracer Course, we had programmers on call to update and modify the website immediately when instructors changed their presentations or added content since the site was used as the live delivery system for the lectures and worksheets.
VI. Data for Evaluation

A. Test and Core Usage

Membership: The MMPC currently has 783 members at 181 institutions. These include clients, MMPC Center personnel and advisors, funding program applicants, awardees and others. Of these, 22 are foreign, from 18 Universities in 10 countries. 31 members are from industry, representing 26 companies. 16 members represent the government (mostly NIH) and the remaining 682 members are at 122 US Universities. Of these, 635 are faculty and the rest are post docs (56), graduate students (28), and technicians (24).

Client base: Among the six MMPCs and their 14 test cores, they served more than 575 clients between 2006 and 2009 (these are likely not all unique). Clients placed 1010 orders for services. The MMPCs report over 75,000 separate tests, but this is very clearly an underestimate. It is also not a very useful number, as some of these are complex, multi-parameter in vivo tests, and some of these represent a single plasma analyte. As examples, more than 3300 insulin clamp experiments were done in the last 3 years, there were more than 3600 indirect calorimetry energy balance experiments, and more than 16,000 body composition analyses. These estimates are based on Center progress reports and details are found in the Center sections of this report (section V).

Strains studied 2006-2009 (incomplete):

<table>
<thead>
<tr>
<th>Strain</th>
<th>Phenotype Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>129S1/SvImJ</td>
<td>5HTR2c/-/ ACAT -/- ACC2 KO ACoA synthase KO</td>
</tr>
<tr>
<td>ACSL-1 KO</td>
<td>Ad-GPAT AdPla ko Alb:GAD34 tg Aldosterone synthase -/-</td>
</tr>
<tr>
<td>Angiogenesis Inhibiting Protein</td>
<td>aP2 -/- Apo E KO ApoAI overexpressor ApoC3 TG</td>
</tr>
<tr>
<td>AT1R +/-</td>
<td>at-PEPCK +/- B10A-uMT Bad KO BCAT -/-</td>
</tr>
<tr>
<td>bGPA</td>
<td>C57BL/6-db/db C57BL/6-ob/ob C57BLKS/J-db/db Calpain 10 KO</td>
</tr>
<tr>
<td>CAMK4 ko</td>
<td>CCK CD1 +/- CD36 +/- CD36/ob/ob</td>
</tr>
<tr>
<td>CD81 ko</td>
<td>Clic5 COX 1 +/- COX 2 +/- CPT1c KO</td>
</tr>
<tr>
<td>Desnutrin TG</td>
<td>DKK agonist DKK2 ko-RC DLK Egr1 KO</td>
</tr>
<tr>
<td>ErbB3 +/-</td>
<td>ErbB3 overexpressor Estrogen in OB/OB FAT Trans KO FGF19</td>
</tr>
<tr>
<td>FLP, Lipin</td>
<td>Foxo Notch KO G6pc2 +/- GAB2 GATA4</td>
</tr>
<tr>
<td>GC tg mice</td>
<td>GDH ko GDH mutant Tg GDH tg GIP/DT</td>
</tr>
<tr>
<td>GLP1R +/-</td>
<td>GLUT4 +/- GLUT4 IR ko GLUT4 overexpressor GPAT KO</td>
</tr>
<tr>
<td>HFABP +/-, +/-</td>
<td>HKII +/-, overexpressor HNF6tg IAP KO IGFBP2</td>
</tr>
<tr>
<td>INDY ko</td>
<td>Integrin a1/-/ Integrin a2/-/ IRS1 KO IRS1/2 DKO</td>
</tr>
<tr>
<td>IRS2 KO</td>
<td>JAZF1 ko</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>LDLR-/-</td>
<td>Leptin receptor ko</td>
</tr>
<tr>
<td>LLF15 KO</td>
<td>Low Phosphate</td>
</tr>
<tr>
<td>Mac FoxP</td>
<td>MafA-/-</td>
</tr>
<tr>
<td>MCAT overexpressor</td>
<td>mCAT tg</td>
</tr>
<tr>
<td>MKP5ko</td>
<td>M-PGC1 b Tg</td>
</tr>
<tr>
<td>Nalp1 ko</td>
<td>NFKB1/-</td>
</tr>
<tr>
<td>p66Shc/-</td>
<td>PA1 -/-, overexpressor</td>
</tr>
<tr>
<td>PKCq/-</td>
<td>PKC-theta KO</td>
</tr>
<tr>
<td>PPAR /RGL KI</td>
<td>PPAR /RGL Ko</td>
</tr>
<tr>
<td>Quadruple</td>
<td>Ralbp1 ko</td>
</tr>
<tr>
<td>SGLT2</td>
<td>SHP2 ko</td>
</tr>
<tr>
<td>Stat3 ko/SIRT1 ASO</td>
<td>STAT6/-</td>
</tr>
<tr>
<td>TUG UBX-RC</td>
<td>TUG-RC</td>
</tr>
<tr>
<td>UCP3 Tg</td>
<td>VEGF-A/-</td>
</tr>
</tbody>
</table>

**Published papers:** The database reports 191 papers for the years 2006-2009, out of 337 total for all years of the MMPC (https://www.mmpc.org/shared/publications.aspx). This data is gleaned by automated searches of pubmed for the MMPC grant numbers, and through self-report to the database by MMPC users and Center staff. The Centers report 235 papers in progress reports during the same period.

**Grant applications requesting funds for MMPC services:** There are few tools available for identifying NIH grant applications that propose to use the MMPCs. A text search through the summary statements and abstracts of submitted NIH grant applications for the words ‘MMPC’ or ‘mouse metabolic phenotyping center’ yield the following information. This is likely an underestimate assuming that for most applications a request for funds for MMPC services would not be noted in the summary statement or abstract.

<table>
<thead>
<tr>
<th>Financial Year</th>
<th>NIH Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>24</td>
</tr>
<tr>
<td>2007</td>
<td>23</td>
</tr>
<tr>
<td>2008</td>
<td>34</td>
</tr>
<tr>
<td>2009</td>
<td>21</td>
</tr>
</tbody>
</table>

**Utilization and Capacity for Tests by Category:** Several questions should be asked about the test cores that comprise the MMPC.
1. Are the categories of tests appropriate and do they meet the current needs of the mouse research community?
2. Is the quality of tests and service to the community adequate?
3. Is the capacity of the core appropriate for the needs of the community?
4. Is the level of use of the core appropriate for the capacity and for the needs of the community?

The best way to answer questions 1 and 2 is to ask MMPC users, advisors, and others in the research community. A synopsis of user surveys and interviews is found in section VI.B and Appendix D. The core capacity and test volume differs considerably across the MMPCs for many reasons. Some of the tests have very high demand, others less. Some of the cores have been in place for a number of years with a well established client base, others are new and are still developing their client base. Some conduct very high throughput tests (thousands of samples per month), others are extremely low throughput (20 animals per month).

Currently, it is difficult to assess whether there are mismatches between core capacity and the demand for its tests, because the current version of the database was completed within the last year and Centers are not current on data entry yet. It will become trivial to monitor core use at any point in time once the database is up to date, and Center personnel are working to bring administrative procedures in line with the database administrative tools and the need for test data entry. Below is a snapshot of database population on July 17, 2009 for the entire consortium, implying that only 8% of orders have been completely entered for the work done over the last 3 years.


| Accepted Orders | 66  |
| Complete Orders  | 340 |
| Experiments with data entered | 83  |
| Animals with recorded data | 1272 |
| Strains with recorded data | 16  |
| Publications     | 191 |

The following is a qualitative analysis of use of the various types of tests over the past three years.

Tests: **Analyte and Hormone Concentrations**
Offered: Case, Cincinnati, Vanderbilt, Washington, Yale

<table>
<thead>
<tr>
<th>Test</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty Acyl CoAs</td>
<td>458</td>
<td>474</td>
<td>645</td>
</tr>
<tr>
<td>Diacylglycerol</td>
<td>490</td>
<td>633</td>
<td>1004</td>
</tr>
<tr>
<td>FFA</td>
<td>1183</td>
<td>872</td>
<td>1560</td>
</tr>
<tr>
<td>TG</td>
<td>596</td>
<td>977</td>
<td>2215</td>
</tr>
</tbody>
</table>
Analytical cores are in general in very high demand. These cores measure hormones (insulin, glucagon), incretins (GLP-1, GIP), cytokines (leptin, adiponectin), cholesterol and lipoproteins, lipids, amino acids and carbohydrates, acyl-CoAs, methylmalonyl-CoA, citric acid cycle, gluconeogenesis and glycolysis pathway intermediates, ions, and measure stable and radioactive isotope enrichment. They routinely measure some enzyme activities (acetyl-CoA carboxylase, malonyl-CoA decarboxylase). They do these measurements in plasma and tissue extracts. Tissue/plasma can be sent to the MMPC rather than live mice for these tests.

Tests: **CNS and Brain Metabolism**
Offered: Case, Cincinnati, UTSW, Washington, Vanderbilt

<table>
<thead>
<tr>
<th>Test</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain blood flow</td>
<td>0</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>TCA cycle, neurotransmitter turnover</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These services are in low demand right now, but given the intense focus on the role of brain as the clearinghouse for metabolic regulation and its importance in obesity and diabetes, interest in these and similar tests may increase over the next years. The MMPC currently offers hypothalamic gene expression analysis, brain substrate uptake and blood flow, cerebral ventricle cannulation, and TCA cycle flux and neurotransmitter turnover (GABA, Glutamate).

Tests: **Cardiovascular and Renal Function**
Offered: Washington, Vanderbilt, Cincinnati, UTSW

<table>
<thead>
<tr>
<th>Test</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Pressure</td>
<td>77</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Tail cuff manometer</td>
<td>257</td>
<td>680</td>
<td>1254</td>
</tr>
<tr>
<td>Telemetry</td>
<td>1048</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>Echo</td>
<td>365</td>
<td>719</td>
<td>886</td>
</tr>
<tr>
<td>Invasive Hemodynamics</td>
<td>0</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Aortic Banding</td>
<td>0</td>
<td>82</td>
<td>2</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
<td>145</td>
<td>190</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>92</td>
<td>231</td>
<td>253</td>
</tr>
<tr>
<td>Arterial Injury</td>
<td>0</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Urine Albumin and Creatinine</td>
<td>142</td>
<td>176</td>
<td>154</td>
</tr>
<tr>
<td>Urine Osmolarity</td>
<td>0</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>
Kidney Transplant 0 0 3
Glomerular Filtration Rate 14 0 0

Washington, Vanderbilt and Cincinnati have full service heart function cores. They provide non-invasive or invasive measures of blood pressure and heart rate, vascular and cardiac contractility, echocardiography and electrocardiology measures, left ventricular pressure and cardiac output, atherosclerosis and carotid artery injury. UTSW measures myocardial metabolism: heart substrate oxidation (glucose, fatty acids), TCA cycle flux and anaplerosis. Vanderbilt offers kidney function tests. The organ function cores still seem to be underused, although blood pressure, echo, infarction studies and atherosclerotic plaque estimation are seeing increasing demand. The kidney function tests are less popular.

Tests: **Energy Balance**
Offered: Cincinnati, Case, Washington, Vanderbilt, Yale

<table>
<thead>
<tr>
<th>Test</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food Intake</td>
<td>146</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>Body composition by Proton NMR</td>
<td>3447</td>
<td>2524</td>
<td>7661</td>
</tr>
<tr>
<td>Indirect Calorimetry and double label(EE)</td>
<td>1535</td>
<td>1019</td>
<td>1093</td>
</tr>
<tr>
<td>Body Temperature</td>
<td>25</td>
<td>38</td>
<td>45</td>
</tr>
</tbody>
</table>

These tests are in very high demand and are offered at five of the Centers. In particular, body composition (measured non-invasively in awake animals by an MRI method) and energy balance by indirect calorimetry or doubly labeled water are in high demand. The MMPC is planning to expand capacity in these areas. Food consumption and meal pattern analysis, continuous measure of body temperature, spontaneous activity, exercise tolerance, capacity and metabolic effects of exercise are also offered.

Tests: **Insulin Sensitivity and Glucose Metabolism in the Whole Body**
Offered: Yale, Vanderbilt, Case, Cincinnati, Washington

<table>
<thead>
<tr>
<th>Test</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euglycemic clamp</td>
<td>1258</td>
<td>756</td>
<td>1085</td>
</tr>
<tr>
<td>Hyperglycemic clamp</td>
<td>120</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>Hypoglycemic clamp</td>
<td>20</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>Glucose tolerance tests</td>
<td>32</td>
<td>77</td>
<td>43</td>
</tr>
<tr>
<td>Activity</td>
<td>35</td>
<td>0</td>
<td>19</td>
</tr>
</tbody>
</table>

These tests are in high demand and the MMPC has sought to increase our capacity in this area. The major locations for insulin clamps are at Yale and Vanderbilt, but others are starting to do these with a low volume for now. These tests include hyper- and euinsulinemic, hyper- eu- and hypoglycemic clamps, oral, intravenous and intraperitoneal glucose tolerance tests, insulin tolerance tests, insulin, c-peptide and hemoglobin A1c measures.
Tests: **Intermediary Metabolism and Pathway Flux Kinetics**  
Offered: Case, Texas

<table>
<thead>
<tr>
<th>Test</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acid synthesis</td>
<td>0</td>
<td>0</td>
<td>235</td>
</tr>
<tr>
<td>Protein synthesis</td>
<td>0</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>Glycerol flux</td>
<td>0</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>Glucose flux</td>
<td>0</td>
<td>0</td>
<td>140</td>
</tr>
<tr>
<td>Metabolite Profile</td>
<td>0</td>
<td>0</td>
<td>155</td>
</tr>
<tr>
<td>Cardiac Insulin Action</td>
<td>30</td>
<td>0</td>
<td>256</td>
</tr>
<tr>
<td>Isotopomer analysis of tissue extracts</td>
<td>20</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Liver Glucose production</td>
<td>50</td>
<td>94</td>
<td>215</td>
</tr>
<tr>
<td>Liver TCA flux</td>
<td>50</td>
<td>94</td>
<td>215</td>
</tr>
<tr>
<td>Liver Substrate oxidation</td>
<td>50</td>
<td>94</td>
<td>230</td>
</tr>
<tr>
<td>Heart Substrate oxidation</td>
<td>40</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Heart TCA cycle flux</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Heart Triglyceride synthesis</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liver Triglyceride synthesis</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tissue High energy phosphates</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Endogenous glucose production</td>
<td>20</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>In vivo sources of plasma glucose</td>
<td>50</td>
<td>20</td>
<td>120</td>
</tr>
<tr>
<td>In vivo hepatic TCA cycle turnover</td>
<td>20</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Endogenous ketone turnover</td>
<td>0</td>
<td>10</td>
<td>120</td>
</tr>
<tr>
<td>Endogenous urea turnover</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Imaging studies</td>
<td>0</td>
<td>30</td>
<td>50</td>
</tr>
</tbody>
</table>

Two of the MMPCs focus on measures of intermediary pathway analysis using Mass Spectrometry (Case) or NMR (Texas). These two technologies are complementary. These measurements were in low demand when the MMPC began in 2000 but interest has been steadily building to the point where the capacity of the cores has or will be reached soon, given that they tend to be time-consuming and expensive. These include protein, lipid and carbohydrate synthesis and turnover, TCA cycle flux or substrate oxidation in heart and liver, gluconeogenesis, organ specific or whole-body protein, lipid and cholesterol synthesis.

Tests: **Islet function and inflammation**  
Offered: Yale, Vanderbilt, Washington  
Islet isolation and insulin secretion are available at Yale and Vanderbilt. These tests have a low demand.

Tests: **Lipid absorption and metabolism**
Offered: Cincinnati, Case, UTSW

<table>
<thead>
<tr>
<th>Test</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat Absorption</td>
<td>456</td>
<td>439</td>
<td>144</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>379</td>
<td>952</td>
<td>1647</td>
</tr>
<tr>
<td>Lipoproteins</td>
<td>2378</td>
<td>2378</td>
<td>327</td>
</tr>
<tr>
<td>Lymph Fistula</td>
<td>0</td>
<td>0</td>
<td>161</td>
</tr>
<tr>
<td>Cholesterol Absorption</td>
<td>0</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Cholesterol Synthesis</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>

The Cincinnati MMPC has a focus on lipid metabolism and uniquely measures gut fat absorption and apolipoproteins. Several MMPCs measure lipid profiles in plasma, and Case and UTSW also measure fatty acid synthesis flux and fat oxidation. These tests are in moderate demand at this point, but demand has been steadily increasing and given the recent focus on lipids in diabetes and obesity, these cores may enjoy more attention in the coming years. In particular, it is expected that demand will increase for the lymph fistula and fat absorption tests.

Tests: Surgery—Catheter Placements, etc.
Offered: all MMPCs
All MMPCs have surgical procedures that can be ordered as tests. These include the placement of arterial and jugular vein catheters, telemetry probes and minipumps. These are generally ordered as part of another test, such as whole body lipid turnover study or an insulin clamp, and are therefore in very high demand.

Tests: Tissue Histology and Morphometry-Kidney and Eye
Offered: Washington, Vanderbilt, Case

<table>
<thead>
<tr>
<th>Test</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Processing and Sectioning</td>
<td></td>
<td>12</td>
<td>533</td>
</tr>
<tr>
<td>Kidney Glomerular Size</td>
<td>0</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>0</td>
<td>101</td>
<td>263</td>
</tr>
<tr>
<td>Movats</td>
<td>0</td>
<td>14</td>
<td>232</td>
</tr>
<tr>
<td>Silver Methanamine</td>
<td>0</td>
<td>28</td>
<td>166</td>
</tr>
</tbody>
</table>

The Washington MMPC has a focus on kidney histology and morphometry for diabetic nephropathy studies. They also study retinopathy. Kidney histology is in particularly high demand, partly because of the AMDCC mouse models of diabetic complications. Vanderbilt also has a tissue pathology subcore.

Tests: Other
Confocal imaging of in vivo function (microvascular blood flow) and gene expression offered at Vanderbilt. This has a low demand and is expensive and time consuming, but may be very valuable when needed. Core staff are working to automate the analysis of this data in order to improve throughput.
B. User Satisfaction Survey

A survey was sent to all MMPC clients who were associated in the database with completed tests in the last two years, and 64 responses were received. The complete results are found in Appendix D and at http://www.genomics.mcg.edu/SelectSurveyNET/ResultsOverView.aspx?SID=M83HJ69ZY27NT45. The following questions were asked, and data are summarized here.

1. *Which National MMPC was used for this order of tests?* Most responses used Yale, Vanderbilt and Cincinnati, as these are the established Centers and have the highest order rate at this point.

2. *Please tell us your biomedical field of interest?* Interests ranged across 33 topics, mostly in diabetes, obesity, nephropathy, cardiopathy, liver, inflammation, cancer and neurology.

3. *Please rank your level of expertise in metabolic and physiologic phenotyping on a 7-point scale, with 1 being the lowest level of expertise and 7 being the highest* Clients tend to be sophisticated with only 10% at the lowest expertise levels 1-2, 30% at level 3-4 and 61% distributed evenly among levels 5-7.

4. *Please rank your level of agreement with the following statements regarding the Center that completed your order.* Clients felt center staff were courteous, helpful and knowledgeable (90% of respondents agree). 75% felt that the tests were done in a timely fashion, 89% felt that offered tests were appropriate for their needs. 84% felt that center staff adequately answered questions about data, and 87% felt that the overall experience with MMPC was positive.

5. *Experience Comments for MMPC.* Of 20 specific comments, 10 were positive. These included praise for the mouse clamping course, good experiences talking and working with Center staff, and reports of important papers that resulted. 10 were negative, and commented that cores were booked resulting in a long wait for tests, reported administrative problems in reporting out data, communication problems regarding test protocols or animal concerns, concern regarding intra-assay variability, or frustration regarding the collaborative rather than fee-for-service nature of their experience.

6. *Statements about the MMPC website* 63% felt that the content quality is satisfactory, and only 5% disagreed. 51.5% feel the site is easy to navigate, whereas almost 10% had problems. 60% were able to find the information they wanted, but 6.5% couldn’t. 43.5% found placing an order from the website easy, whereas 6.5% had problems.

7. *Experience Comments for MMPC website* 7 comments suggested simplifying web content and navigation, requested more test information and personalized test ordering, and noted some conflicts between the Center and National websites.
8. **Problems with animal/tissue handling.** Of 64 respondents, 4 report problems with shipping animals or tissues to the Centers, and 1 experienced animal care or sample storage problems.

9. **Please describe any problems you encountered.** Long quarantine times, misunderstanding regarding animal diet, shipping company problems, had to send samples to two Centers to get all needed assays done. 2 reported that animals were shipped to MMPC, tested, and shipped back home without incident.

10. **Did you publish the data?** Of 62 respondents, 24 have published data, 8 will not publish, and 34 plan to publish.

11. **Did you use the data for a grant application?** Of 62 respondents, 31 used data for a grant application, 11 have not, and 20 plan to use it to apply for funding.

Overall, survey responses are positive and indicate where improvements can be made.
C. Johns Hopkins School of Business Evaluation—Synopsis and Recommendations

The MMPC submitted a proposal to the Johns Hopkins University School of Business requesting that its business plan be evaluated as a final “Capstone” project by MBA students seeking their degree in medical business management. Four students undertook the project: Yasmin Abbas, Abby Lipsitz, Tony Richardson, and Karen Rothrock-Dixon. These students visited the MMPCs and met with Center and Core Directors, and administration and business staff. They also conducted surveys at the Centers, and worked with Dr. Maren Laughlin of the NIH in order to generate a report describing and evaluating the strengths, weaknesses, and perceived opportunities and threats to the MMPC business operations. They made recommendations for improving the business aspects of the MMPC, and provided strategies for implementing and maintaining these recommendations and evaluating the outcomes. Tony Richardson continued working on the project following his graduation, in fulfillment of his training through the NIH Administrative Fellows Program. The complete report is found in Appendix E, and the Center business surveys are found in Appendix F. The recommendations for the business plan of the MMPC are reproduced here.

Recommendations

Overall Business Strategy

• To develop a financial sustainability plan
• Develop business outcome measures and targets
• Develop marketing strategy
• Establish a business oriented planning and decision making body or hire a Business Development Specialist to prioritize and implement good business practices

Human Resources

• The workforce is primarily comprised of scientific professionals, Center Directors and Center Co-Directors focused on research. Unlike other business models, it is somewhat one-dimensional in this respect. It would be beneficial if a member of the team or a new position be identified to take on a business practice and planning role of the MMPC as it pertains to business development and marketing.
• The establishment of staff development models that address turnover rates and provide documentation of: Career goal assessments, Quality reviews and training (new and ongoing)

Price Structure

• To implement the use of Activity Based Costing (ABC) to assist in internal and external benchmarking and identifying costs and savings associated with dissemination of best practice. It will also help by identifying the non-value added activities and eliminating them, hence ensuring revenue efficiency achievement.
• To develop a set of costing and pricing principles designed to fully absorb costs of all MMPC services based upon income performance goals and measures. By doing so, discrepancy between different centers is eliminated and thus customer confusion is eliminated.
Accounting and Reporting

• To prepare and issue standardized reporting of accounting/financial statements.
• In addition, workload of each MMPC core is reported cumulatively. This is helpful when obtaining data regarding each MMPC in its totality but it does not give a clear breakout of the performance of individual core businesses in order to assess capacity, utility and profitability. It is recommended that MMPC Cores report data individually as well as cumulatively in order to better identify strengths and weaknesses of each core as it relates to utility of specific testing. In addition, it would provide each MMPC with information to better make data driven decisions as they work to develop, change or maintain specific testing.

Work Flow

• Based on the individual MMPC interviews with Core Directors and operational survey questionnaires, similarities between responses are noted relating to workload, personnel and inventory. There are multiple steps involved in the request and application process for the investigator when ordering a test. Investigators may tend to bypass some of the steps for simplicity and expediency. A detailed uniformed workflow and documentation process should be developed in order to identify proper sequencing and any duplication of the process as well as “non-value added steps”. Making better use of the electronic administrative tools could greatly improve this process.

Client-Center Relations

• Documentation of staff consultation time and effort. This will help to decide if time spent talking with clients is appropriate and help strategize if it is excessive or ineffective.
• There was ambiguity in use of the term of “Collaboration”. A well defined process or policy that is communicated to its purpose and use would clarify this issue.
• Recommend that scientific collaboration and service fees are kept completely separate and transparent. Members of the collaboration can decide who pays the MMPC fees. Documentation of collaboration agreements should be explicit about occurrences of co-authorship.
• Customer base development such as: Newsletters, invitations to symposiums and educational courses.
D. AMDCC Collaboration

Collaborative activities pursued jointly by the MMPC and the AMDCC include:

**Expanding MMPC service offerings for diabetic complications:** The MMPCs provide the scientific community with standardized, high quality metabolic and physiologic phenotyping services. Recognizing the need to apply these principles to phenotyping mouse models of diabetic complications, the MMPC entered into partnership with the AMDCC to identify needs and enhance phenotyping services for the complications research community. As a result, the MMPCs now provide a wide range of tests capable of measuring diabetic nephropathy and cardiovascular disease (http://depts.washington.edu/mmpc/); tests measuring diabetic retinopathy are currently under development.

**Identifying and piloting new phenotyping assays:** In order to bolster research efforts for both diabetic retinopathy and neuropathy, the AMDCC and MMPC worked closely to organize a joint workshop entitled “Advances Toward Measuring Diabetic Retinopathy and Neuropathy” in April 2007. The meeting included presentations describing clinical and animal studies in diabetic retinopathy and neuropathy; current methods for identifying, quantifying, and measuring these complications; and new advances that may lead to improvements in phenotyping these conditions. This workshop provided a forum for identifying needs and research opportunities for both AMDCC and MMPC pilot and feasibility programs. A summary of this meeting was published (Advances toward measuring diabetic retinopathy and neuropathy; from the bench to the clinic and back again (April 4-5, 2007, Baltimore, Maryland). Kern, TS, Berkowitz, BA, Feldman, EL. J. Diabetes Complications. 2009 May-Jun; 23(3):219-23.)

In 2007, the MMPC P&F program was targeted to novel tests in diabetic neuropathy and retinopathy. Two P&F awardees presented their work at the AMDCC meeting in June, 2008. Bruce Berkowitz discussed a novel technique for measuring intraretinal ion activity and retinal thickness in diabetic mice using manganese-enhanced MRI (Invest Ophthalmol Vis Sci Dec 2008). Karel Zuzak presented exciting new data on the use of ‘hyperspectral’ imaging for diabetic peripheral neuropathy and wound healing.

Annual meetings: Representatives from each consortium routinely attend the annual meetings of the collaborating consortium. For example, Dr. Charlie Alpers (UW-MMPC) attended the Fall 2008 meeting of the AMDCC at Baltimore, MD to assist in development of phenotyping protocols for diabetic nephropathy, and Dr. Dale Abel (Head of AMDCC steering committee) attended the annual meeting of the MMPC held in September of 2008 in Seattle. These cross-consortial interactions enhance and help to coordinate the activities of both consortia.

**Phenotyping AMDCC strains:** MMPC PIs Wasserman and Leboeuf have served as advisors in the development of metabolic phenotyping protocols for AMDCC strains. These metabolic assays are now implemented as standard protocols by the AMDCC-linked Mouse Generation and Husbandry Core (part of the Type 1 Diabetes Resource at Jackson Labs; http://type1.diabetes.jax.org/). A unique partnership was forged between the AMDCC and MMPC at the beginning of their second project periods to leverage the phenotyping capability
of the MMPC and apply it to new strains being developed by the AMDCC. To date, 10 AMDCC strains have been forwarded to the MMPCs for phenotyping, with 127 individual mice assayed for measures of diabetic nephropathy and 151 mice phenotyped for cardiovascular endpoints. This unique collaboration has already produced >1000 datapoints describing important characteristics of end organ damage in novel models of complications that can be accessed via the MMPC/AMDCC database.
E. Scientific Progress through the MMPC P&F and MICROMouse Funding Programs
http://www.mmpc.org/shared/fundingPrograms.aspx

The MMPC has enjoyed and benefitted from its two programs that fund small research projects aimed at providing new tests for phenotyping mice, or at understanding disease using mouse models. The MMPC has had a P&F program since its inception http://www.mmpc.org/shared/pilotFeasibility.aspx. For the first five years, each MMPC solicited and funded projects from the home institution and nearby research institutions, and P&F projects from these first years added several cores and tests to the MMPCs. One (fecal fat absorption) was actually tested in humans. The P&F program has been housed in the CBU since 2006, and applications are solicited from across the nation and are not confined to the MMPC institutions. Between $250,000 and $300,000 is set aside annually to fund applications of up to $60,000 total costs. These are submitted June 1 and peer-reviewed, and the Executive Steering Committee selects those considered to be of highest scientific quality at their annual meeting each fall. The MICROMouse program http://www.mmpc.org/shared/microMouse.aspx was added in 2007 and is designed to fund collaborative research projects with or among MMPCs that contribute toward the MMPC goals. Applications come in and are peer reviewed quarterly in order to expedite research. The MMPC executive steering committee chooses projects considered to be of highest scientific quality and program priority for funding.

<table>
<thead>
<tr>
<th></th>
<th>FY2007</th>
<th>FY2008</th>
<th>FY2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>P&amp;F applications</td>
<td>18</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>P&amp;F awards</td>
<td>7</td>
<td>3</td>
<td>in review</td>
</tr>
<tr>
<td>MICROMouse applications (per quarter)</td>
<td>NA</td>
<td>2 total 9</td>
<td>2 in review</td>
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<tr>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>MICROMouse awards (per quarter)</td>
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<td>1 total 5</td>
<td>2 in review</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Total Awards</td>
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<td>8</td>
<td>2 (to date)</td>
</tr>
<tr>
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<td>4</td>
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</tr>
<tr>
<td>Tests added to MMPC</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**P&F Projects FY2009**
Applications have been received and being reviewed.

**P&F Projects FY2008**
*Title:* Quantifying the reaction rates that affect fatty liver and hepatic function  
*PI:* Stephen Previs  
*Institution:* Case Western Reserve University (Cleveland, OH)
Status: ongoing (progress report due October 2009)

**Title:** Proteomic analysis of mouse plasma lipoproteins  
**PI:** Sean Davidson  
**Institution:** University of Cincinnati-Main Campus (Reading, OH)  
Status: ongoing (progress report due October 2009)

**Title:** Live-in gradient layer calorimetry for high throughput metabolic studies of genetically altered mice  
**PI:** Karl Kaiyala  
**Institution:** University of Washington (Seattle, WA)  
Status: ongoing (progress report due October 2009)

**P&F Projects FY2007**

**Title:** Noninvasive evaluation of vascular structure and function in mouse models of metabolic disease: validation studies to establish the usefulness of pulse wave velocity (PWV) and aortic intima-media thickness (IMT) in mouse models of metabolic syndrome.  
**PI:** Attila Kovacs  
**Institution:** Washington University (St. Louis, MO)  
Status: completed

**Title:** MRI Phenotyping of Murine Diabetic Retinopathy  
**PI:** Bruce Berkowitz  
**Institution:** Wayne State University (Detroit, MI)  
Status: completed

**Title:** Monitoring Diabetic Retinopathy Progression in Mice using Hyperspectral Imaging  
**PI:** Karl Zuzak  
**Institution:** University of Texas at Arlington (Arlington, TX)  
2. UC Agarwal, “Characterization of a Non-Invasive Hyperspectral Microscopy Imaging System and visualizing the vascular development of diabetic retinopathy inthe double-knockout apoE/- db/db mouse.” Master of Science Thesis
Status: ongoing (no cost extension)

Title: Lymph Fistula Mouse: A novel model for studying incretin secretion
PI: Phil Howles
Institution: University of Cincinnati (Cincinnati, OH)
Status: this test has been added to the Cincinnati MMPC

Title: Innovations in phenotyping islet function in mouse metabolic disorders: develop a systematic and comprehensive set of fluorescence-image-based tests to assess pancreatic islet health and function for comparing animal models of metabolic disorders.
PI: Craig Nunemaker
Institution: University of Virginia (Charlottesville, VA)
Status: completed

Title: Assessment of Diastolic Heart Function in Diabetic Mice
PI: Elina Minami
Institution: University of Washington (Seattle, WA)
Status: This test has been added to the Washington MMPC

Title: Assessment of Bladder Sensory Threshold in Diabetic Mice: feasibility testing of a prototype of a device that, in conjunction with a commercially available stimulator, Neurometer® CPT/C (Neurotron, Inc.), will allow laboratory scientists and clinicians to test the status of the afferent ANS of the bladder in mice
PI: Firouz Daneshgari
Institution: Cleveland Clinic Lerner College of Medicine of CWRU (Cleveland, OH)
Status: ongoing (no cost extension)

MICROMouse Projects FY2009
Title: Effects of acute deletion of selective transcription factors on mouse islets
PI: Craig Nunemaker
Institution: University of Virginia Health System (Charlottesville, VA)
Papers:
Status: To Be Awarded

Title: Characterization of A New Murine Model of Cardiomyopathy in Type 2 Diabetes
PI: Kevin O'Brien
Institution: University of Washington (Seattle, WA)
Papers:
Status: To Be Awarded

MICROMouse Projects FY2008
Title: Characterization of a New Murine Model of Reversal of Diabetic Nephropathy
PI: Charles Alpers
Institution: University of Washington (Seattle, WA)
Status: awarded 6/1/2009

Title: Leptin-mediated regulation of spontaneous physical activity in mice
PI: Brent Wisse
Institution: University of Washington (Seattle, WA)
Status: Awarded 4/1/2009

Title: Development of a mouse model of diabetic wound healing
PI: Efi Kokkotou
Institution: BETH ISRAEL MEDICAL CENTER (Boston, MA)
Status: Awarded 4/1/2009

Title: Effect of Murine norovirus on the phenotype of LDL Receptor-Deficient mice
PI: Lillian Maggio-Price
Institution: University of Washington (Seattle, WA)

Title: Increased risk for diabetes and obesity in offspring of multiparous mice
PI: Laura Woollett
Institution: University of Cincinnati (Cincinnati, OH)
F. Course Attendance and Evaluations

Isotopic Traces in Metabolic Research: Principles and Practice of Kinetic Analysis
http://www.mmpc.org/shared/tracers.aspx

This annual team-taught course has been held twice so far, October 8-12, 2007 and May 4-8, 2009, both times in Little Rock, AR. It is a collaboration between the MMPC and the University of Arkansas for Medical Sciences Donald W. Reynolds Institute on Aging. The 2007 course was taught by 14 faculty and had 88 students. The 2009 course had 9 faculty and 58 students. The course syllabus is found at http://www.mmpc.org/documents/Tracers_Syllabus.pdf. Students were asked to fill out evaluations, and a synopsis is found in Appendix G. The full evaluation data for the 2009 course is available at http://www.genomics.mc.edu/SelectSurveyNET/ResultsOverView.aspx?SID=R89HF72NG45QA36. The organizers tried very hard to use the results of the 2007 survey to improve the course, and will continue to do so. This course will be offered annually for the next four years, and it will likely focus on different topics each year. Suggested focus areas are protein metabolism, the insulin clamp, mass spectrometry, lipid metabolism. The 2010 course will be held in Cleveland, OH.

Glucose Clamping the Conscious Mouse: A Laboratory Course
http://www.mmpc.org/shared/clamping.aspx

This annual course has been held at Vanderbilt for a week in the late summer/early fall for each of the last 4 years. Course materials are found at http://www.mc.vanderbilt.edu/root/pdfs/mmpc/Manual_MMPC.pdf. 10 students participate each year, and learn the theory behind the clamp, as well as receive practical training in how to do both the surgery and the clamp experiment. It has been extraordinarily popular, and the current waiting list has 48 people on it. A synopsis of the student evaluations for all four years of the course so far is found in Appendix G.
G. Websites and Database

Considerable progress has been made in the last three years on the national website (www.mmpc.org), the individual center websites, and the database. There remain several areas where work continues to be needed.

1. Database search interface needs to be more user-friendly and needs to get people to the data of interest more quickly. The database committee has been recently reconvened to redesign the search front end.

2. Data entry needs to be more complete and more timely. It remains a struggle for MMPC cores to enter data into the database. The CBU staff has been working one-on-one with the Center staff to try and find solutions that meet the unique core needs. Centers need to be encouraged to use the administrative elements of the database, so that orders are entered in a timely and accurate manner.

3. Data parameters and terms need work so that the same parameter name always means the same thing, regardless of test or core, and that different data parameters have distinguishable names. Experiment names need to be unique and meaningful. Standards for naming data parameters and experiments need to be developed and strictly observed.

4. Test protocols need to be detailed and kept up to date.

5. The websites could be used to better effect to communicate about the tests offered at the MMPCs. This is especially true for novel and complex tests, such as those that report on intermediary metabolic fluxes. Easy to follow descriptions of test technology and appropriate applications would reduce the time spent by MMPC staff in consultation with potential Center users.
H. Test Standardization and Validation

The MMPC has published a few papers in which the standard background mouse strains have been phenotyped using major tests. In the early years of the MMPCs, each Center developed its tests in isolation, which was appropriate for the most part since there was relatively little overlap. Considerable effort went into validating nascent technology, especially for very novel, experimentally or conceptually difficult tests such as the NMR measurement of metabolic flux. Test protocols are documented on the websites and in the Test Catalog, and in published papers. However, as more experience has been gained with some of the more complex tests, it has become clear that even small differences in protocols may affect the outcome and interpretation of the data. Examples where this can be true are the insulin clamp procedures, energy balance measured either by indirect calorimetry or by doubly-labeled water, and the invasive and noninvasive in vivo tests of cardiac function. For some tests, the choice of the value of a parameter may depend on the characteristics of the mouse and the specific experiment—a very insulin obese resistant mouse requires far more insulin than a lean one to elicit a given change in glucose uptake, for instance. Therefore, recent attention has focused on producing standard operating procedures (SOPs) for several of the major test categories. Subcommittees with representation from two or more MMPCs have been convened to write SOPs and to elucidate the choice of appropriate experimental parameters in the areas of the insulin clamp, basic carbohydrate metabolism, energy balance, and cardiovascular phenotyping.

Publications Focused on Test Development and Validation


7. Jeffrey N. Rottman MD,1,2,3 Gemin Ni MD,1,3 and Michael Brown, BA. Echocardiographic evaluation of ventricular function in mice. Echocardiography Journal


VII. Evaluation by External Evaluation Committee

The following comments were provided by the members of the MMPC External Evaluation Committee and address the strengths and weaknesses of the current program, with suggestions for the immediate and long-term future of the program. Advisors were also invited to comment on individual Centers as desired. Finally, teleconferences allowed advisors to discuss the major recommendations.

Summary of Recommendations

Clarify the business model—The mission statement and business goals should be reiterated to clarify whether the MMPC is a single entity or six independent businesses, and a financial sustainability plan and outcome measures and targets should be developed from there. Business practices should be standardized over all Centers, including the fee structure and role of collaboration between Centers and clients—this might best be accomplished with substantial top-down involvement. A business director to oversee the entire program might be useful and Center business / administrative staff should take a more prominent role. Standardized reporting and accounting practices should be instituted. Center staff should document the considerable time spent in consultation with clients. There should be standard practices in place for the Centers to set fee schedules and cost recovery approaches that take account of the time for consultation and money for R&D.

Conduct ongoing annual audits/evaluations of Centers—Test/core use statistics should be reviewed annually, and the Center Directors should work with the evaluation board to choose optimum set of tests, provide for better intra-Center coordination, and also potentially try to coordinate with other similar NIH-funded animal phenotyping cores. However, it was clear in discussion that all feel that the Center Director and Core Director’s are empowered to make these sorts of decisions, and have access to the best information on which to base them. As part of goal-setting, the MMPCs should attempt to assess need for their tests and whether the core capacity is appropriate for the perceived needs. Geographic regional needs should be considered.

Center specialization and regional considerations—Currently there is a mix of specialized Centers and ‘one-stop-shop’ type Centers. Choice of tests should be guided by demand for those tests, and emphasis should be placed on regional needs. Some tests with limited demand may require a single core, whereas others need to be offered in more than one site. This requires coordination to determine need and tailor offerings to need. It is important to consider regional needs, especially for tests done on live mice. These tests in particular may need to be done in more than one Center and distributed among the coasts and center of the country.

Improve advertising and outreach—There are several suggestions aimed at improving the community’s knowledge of the MMPC. For instance, there could be a bigger presence for MMPC at scientific meetings. MMPC has presented posters and symposia at national meetings, and it should also provide slides about the MMPC and on test protocols for clients to use in their talks when presenting data taken at an MMPC. The MMPC could take
advantage of NIH-sponsored meetings and workshops for young PIs to encourage them to take advantage of the services. The MMPC should improve the websites and use them more effectively to educate users regarding the test technology and interpretation. Missing test descriptions/protocols should be provided. The MMPC has published some papers on standardization and comparison of tests, and has a few more planned for 2010 publication, and should continue to write high profile papers on protocols and do head-to-head comparisons of similar tests. The MMPC could also write newsletters for distribution to the MMPC membership. MMPC should assess whether the cores are underutilized, and this should guide marketing. Geographical regions should be kept in mind here, and there may be a use for regionally targeted marketing.

Reduce barriers to testing—currently the turn-around time for studies on living animals is limited by required quarantine time, and there may be solutions for reducing this. Each Center should be able to conduct a small set of standard tests including body composition and energy balance.

Protect Center Staff Careers—It is important to provide incentives and career advancement opportunities for Center staff, especially Core Directors. There is an important role for, and an opportunity for consortium publications and collaborative publications. The MMPC must clarify the business model so that the Centers are economically healthy and the staff retains academic rewards.

Compare and develop technology—the P&F program might be used to encourage careful comparisons between technologies, such as double-labeled water and calorimetry to measure energy balance. This work should be published in high level journals.

Potential new scientific areas for years 11-15

- Nutrient sensing in the brain. Fatty acid metabolism in regions of the brain clearly involved in sensing changes in dietary composition. Interaction between nutrient sensing neurons and other brain regions. A suggestion is to have a P&F RFA for mouse functional brain imaging studies, and to invite imaging experts to an annual meeting.
- Adipocyte biology. Bioimaging approaches to protein interactions on lipid droplets, lipid metabolism, etc.
- Bariatric surgical models.
- Microbiome/metabolomics of microbiome.
- Mitochondria biogenesis and function
- Interface between metabolic disease and cancer
- Trauma/sepsis and the interaction with metabolic disease

Advisor #1 Written Comments

The JHU School of Business Evaluation and Report was most informative in providing evidence and opinions regarding the function of and outlook for the MMPC program and its individual Centers. While the Centers and its Coordinating unit were viewed highly favorably,
certain deficiencies were outlined in terms of the sustainability of the Centers as service providers to the scientific community.

Potential Resolution of Fee Structures and Co-authorship Issue
The diversity of the Centers’ provided services was considered a strength and a weakness. There is a large variety of services and each Center has unique services that defines the unique properties of the individual Centers. However, there are several areas where there are very few or no users, suggesting that the Centers should review their services as a lack of interest. This ties in to the fee structure that is provided. One suggestion that should be entertained is to make a uniform fee for services common to all of the Centers. As for those services that are rarely used but require the attention of the Core Directors, this should be considered as an opportunity for co-authorship in that the establishment of a fair fee would be difficult.

Annual Evaluation of Services and Users
The Centers most likely should establish an annual survey and review of their users in terms of the services that are available and future needs might also be anticipated. This review should also have the role of eliminating unused services and adding newly requested services that are within the capabilities and purview of the Centers. While an arbitrary number of users might be set for a given service, it would be better to place this at the discretion of the Center Director and reviewed by the MMPC Board.

Recruitment of External Users
Some Centers have numerous internal and external users. While it is understandable that internal users (internal to the Center’s institution) would make up the bulk of the users, the MMPC program should be viewed as a national resource. It is likely that many investigators have established individual or institutional resources that serve a similar function. Thus, these investigators may not be attracted to use the Centers and may actually be viewed as competitors to the MMPC Centers. It is also possible that these resources may actually be funded by NIH as components of other specialized Centers. It is likely that there should be some consideration for coordination between the MMPC and these other Centers and investigators.

New and Innovative Technologies
Services that are provided will become attractive to users if they are considered to be necessary and/or current state-of-the-art technology. This is influenced by the usage of these technologies in publications that are highly regarded and/or cited. Thus, the Centers’ staff should understand this association: that the adoption of new and innovative technologies will be fostered by their inclusion in publications within high impact and high profile journals. Demand will be fostered by the foundation of these publications while widespread application by the community will depend upon the utility, robustness and ease of use of the specific technology. This reviewer does not believe that cost is a major issue for adoption of novel technologies and could represent one means by which cost recovery could be attempted upon wider acceptance. Development costs for a novel service could be attempted upon introduction of a service while the development team would have benefited from the publication(s).
Competition Between Centers

There is an inevitable degree of competition between Centers as well as competition during the renewal process. This inherent instability is built into the system and, while it may be counterproductive, is inevitable. Countermeasures to this instability would be the establishment of a fee structure and cost recovery that would enable the Center to be self-sustaining. Thus, there is greater incentive for the Centers to re-establish a fee structure that is commensurate with the actual costs of the services.

Advisor #2 Written Comments

The evaluation provided by the External Advisors in Sept 2004 can be distilled into the following 4 basic areas:

1. Outreach and Education - This item is broad and involves informing the scientific community of the services that are available at MMPC sites and educating these users as to which services/assays can best be used to understand the phenotype of their mouse model.

2. Accessibility to Services of MMPC Sites - The difficulty of transferring mice from user labs to centers and between centers was identified as an impediment to utilization of MMPC sites by the scientific community.

3. Protocol Description/Methods Documentation/Test Standardization among MMPC Sites - The need to have clear, concise descriptions of available procedures/tests with links to detailed protocols and publications was recognized, along with the need to adopt best practices for specific tests (i.e. clamps, energy expenditure) and standardize the protocol for such complex procedures among Center sites.

4. New Opportunities & Expansion of Phenotyping Capabilities - The need to keep abreast of the development of new concepts/approaches in the field, as well as technological advances that provide access to new phenotyping methods.

These issues have been addressed during the intervening 5 yrs and detailed responses have been provided in the “Evaluation Report to the NIDDK Advisory Council” which describe the steps taken to enhance the overall value of the MMPC to the research community. The following comments/suggestions are offered from the prospective of what remains to be done to further enhance the ability of the MMPC to achieve its core goals. These comments will be organized within the context of the 4 basic areas identified above.

Outreach and Education - Many within the scientific community who work with animal models of obesity and/or diabetes continue to be unaware of the MMPC consortium and its collective capabilities with respect to metabolic phenotyping of mice. In some cases, the researchers are aware of the MMPC but have no understanding of how it functions, how the services can be accessed, or how to approach using the services to phenotype their animal model. Therefore, expanding awareness of the MMPC within the scientific community continues to be an important goal going forward. This objective is very broad and the
following suggestions are offered as potential ways to supplement current efforts and increase overall awareness and utilization of the MMPC.

A. Provide users of MMPC services a slide template that can be used to acknowledge the MMPC when the PI is presenting his/her data in a seminar. This has the potential to reach scientists where the PI has been invited to speak that are also working in the areas of obesity/diabetes. (For example, when presenting the clamp data generated at the Vanderbilt MMPC, I mention that we solved the logistics problem of animal transfer by having animals shipped directly to them from Jackson Labs and the formulated diets sent to them from the manufacturer.)

B. Develop strategies for communicating with groups of young investigators who can be reached through program networks. For example, NCRR sponsored Center Grants called COBREs are designed to mentor promising young junior investigators to independence by building intellectual and technological infrastructure at host institutions. A key goal of the COBRE/INBRE collective is to share information and make junior investigators aware of technical resources and complementary infrastructure within the network of NCRR-sponsored COBREs. Each of the different COBREs are organized around a specific scientific theme (i.e. the PBRC COBRE is obesity/diabetes), and while the themes of some COBRE sites would not be relevant to the MMPC mission, many would. With the Pennington COBRE, we emphasize to our junior investigators the importance of developing a translational component in their grant proposals. Therefore, I think the COBRE programs around the country would be ideal targets for outreach activities by MMPC Program Staff. There are yearly meetings of the COBRE PIs from different regions of the country. Perhaps NCRR program officials could be approached about attendance/presentations at these meetings.

C. The MMPC Main Page and the Web pages of individual MMPC Centers serve many purposes. They represent an important point of contact with the research community and the key portal to the information needed for individual researchers to make decisions about using MMPC services. The collective Web sites have been improved significantly during the last 5 yrs to address recommendations provided in the previous review. Specific comments for additional consideration are provided below as bullet points.

1. The MMPC main page provides a link to a list of publications that acknowledge the MMPC for supporting/conducting in part the work reported in the publication. However, beyond providing pubmed links to the individual publications, the list just shows that the services/tests of the individual MMPC sites are being used. The list would be far more useful if it could be sorted in various ways to identify which service/test of the MMPC was used and the site where the work was done. For some of the more complicated procedures and tests, this would provide the potential new user of the MMPC a far more informative reading of the associated manuscript. The reader could see how the authors used the procedure/test to address the question they were asking. The Yale site provides a link to the same list of publications as the MMPC main page, but there were no additional sorting capabilities present. The UTSW Center provides a link to publications but the link was nonfunctional. The remaining MMPC sites did not provide links to publications, although the Vanderbilt site did contain lists of publications that addressed practical considerations.
regarding choice of mouse strain and technical details of the procedure. This aspect of the MMPC main page and individual sites could be substantially improved, and it would have the dual benefit of bringing better informed new users to their initial discussions with MMPC site core directors.

2. One of the recommendations provided in the previous review (2004) was the need to provide a clear, concise description of available procedures and tests offered at each MMPC site. The MMPC Main Page provides links to many but not all of the procedures available at all Center sites. It would be useful to continue updating this aspect of the MMPC main page, along with some utility to identify which sites perform each test. It might also be worth considering providing the link to these protocols in a more prominent position on the main page. Descriptions of protocols are also provided at individual Center Web sites but this aspect of the presentation could be improved by implementing a more uniform path to protocol descriptions among all sites.

3. The use of model slides to provide a visual illustration of certain protocols and tests could be useful in educating new investigators coming to MMPC Web sites and helping them decide which tests and procedures are needed to address their question. Providing links to relevant manuscripts where the procedure was used, alongside each illustration, would allow new investigators to become informed in the most efficient manner and potentially save Core Directors time providing this information orally to new investigators. The UT Southwestern MMPC site provides a schematic flow chart showing how the various procedures are organized and the type of data they provide. The functionality of the schematic is not yet online, but the diagram is very effective in communicating how the various procedures/tests are organized between in vivo and in vitro approaches. Further development of this approach using diagrams of metabolic pathways being studied would be extremely useful for stable isotope studies and show how the labeled compound or element traverses the pathway being studied. By highlighting the stable isotope used to study fluxes through pathways with a different color in these diagrams, the MMPC user is able to visualize how the experimental protocol functions to measure what is occurring within the pathway. Again, the added benefit of developing these images for the MMPC sites are better informed MMPC users who require less maintenance by MMPC site Core directors.

4. The ability to search the database of previously conducted procedures/tests, sorting by mouse strain, procedure, diet, etc is present to some extent on the MMPC home page but it is not functional to the extent necessary to make it a practical interface or valuable tool. The links to analyze the data (i.e. ANOVA and basic statistics) are good ideas and would be far more useful if the initial search interface was more user friendly. Improving the functionality of this aspect of the MMPC main page and all the Center site web pages will be very valuable to the scientific community and also to new investigators wishing to establish what has been done. This goal should be a high priority going forward.

Protocol Description/Methods Documentation/Test Standardization among MMPC Sites

A. There is substantial heterogeneity in the scientific literature with respect to how data collected by small animal indirect calorimetry (IDC) should be analyzed and
presented. The problem stems from comparisons of animals of different size, or body composition, and the need to take these differences into account when calculating rates of energy expenditure for the groups. As discussed at the last MMPC Steering Committee meeting in Seattle (2008), a consensus should be developed by the MMPC for comparing energy expenditure data from IDC experiments. Given that several MMPC sites now offer measurement of energy expenditure by IDC, it should be a high priority item to reach a consensus on the method of best practices for analysis of this type of data.

Advisor #3 Written Comments

Strengths
1. The availability of a wide variety of tests to the scientific community that most investigators do not have the capability to perform.

2. The reasonable cost structure and, in most cases, the lack of need to include center personnel as collaborators.

3. The ability to have a number of tests performed at the same center (“One stop shopping”)

4. Availability of funds for pilot research projects, either to develop new techniques or to obtain preliminary data for grant submissions.

5. Courses to help educate potential core users.

6. Adequate funding for a highly functional website.

Weaknesses
1. Uneven performance of centers. Some centers have very high throughput and number of users, whereas others are apparently mostly limited to a few investigators in their home institution. The more complex analyses have very few outside users.

2. In some cases the goal of the center is unclear- is there a financial goal to run it as a business, or is taking in money an afterthought?

3. Courses are limited and may not be targeted at the right level to draw users. This is relevant to the most sophisticated tracer methods.

4. Poor incentive for investigators providing core services. Criteria for promotion are unlikely to be met by investigators providing core services without collaboration.

5. Overall model is unclear regarding duplication of services. Some assays are provided at more than one center, some at only one center. At some centers “one stop shopping” would seem to be a feasible goal, whereas this is not a goal at other centers.

6. Uneven outreach to investigators. Some centers have a wide distribution of investigators from across the country, whereas others are entirely servicing their own institution.
7. Website is not as effective in attracting users as might be anticipated.

Immediate Opportunities.
Clarify the culture of the MMPC and the component centers. While the overall goal is clear, specific issues should be clarified as a mission statement and all centers should be evaluated accordingly. In particular is the mission it to perform innovative research or primarily to provide service in the form of routine analyses to the scientific community? Further, is the service meant to be for the general scientific community or to primarily serve the researchers within the institution at which the center is located? Is the financial goal to break even or to make money (as the business plan suggests), or is raising money an afterthought? Are centers meant to provide one stop shopping with a variety of tests, or ultimately is there a goal to ship mice from one center to another?

Within the context of the overall goals of the MMPC, ongoing evaluation could help to keep each center on track. There is a wide discrepancy in the performance of centers, not only in the number of tests performed and investigators supported, but in the nature of the tests. Some centers are developing extremely sophisticated tests used by few, in any investigators outside of the institution, whereas other centers serve a wide range of users across the country with pretty straight-forward tests.

Coordination of tests offered at the various centers would be useful, in conjunction with clarification of the culture of the MMPC. Some tests are offered at several of the centers, whereas others are available at only one center. It should be clear if each center is expected to develop as many tests as possible, even if they already exist at other institutions, or to focus on specialized tests that only they can do.

Personal Commentary
It seems that, excluding the Vanderbilt center, very little money is brought in from outside users, but charging nonetheless defines the culture of the program. The mindset of an investigator paying for a service is quite different from a collaborator. Further, the restriction on collaboration for center core leaders makes participation in the center activities by researchers counterproductive for career development. This is why I think a decision should be made one way or the other- make this a real business with appropriate marketing, standardizing of costs and services, etc, or make it a free service available on a collaborative basis. If it is to be run as a business, then emphasis should be on providing services that are widely used and relatively cheaply provided, whereas expensive, underutilized services should be eliminated.

Advisor #4 Written Comments
Strengths:
MMPCs have been very active. The six MMPCs have collectively performed more than 400,000 assays over the last 3 years. Although many of these are accounted for by service to investigators at the home institutions, a significant number of assays have been performed for investigators at other institutions. This high volume of activity attests to the fact that these centers have become an important resource in the research community.
MMPCs serve important educational roles in the research community. In addition to the assays performed, each MMPC serves an important educational role in the obesity/diabetes/lipid metabolism research fields. This educational role takes many forms. Some centers offer formal hands-on courses to instruct investigators to perform specialized techniques such as the use of glucose clamps and isotope tracers in metabolic research. These courses have been met with highly positive response from attendees, who are now empowered to perform these techniques in their own laboratories. In addition, course participants become knowledgeable colleagues and reviewers who will help ensure that work in the field meets a specific standard. A second educational mechanism is the informal consulting/teaching that occurs between investigators and MMPC personnel regarding experimental design and interpretation. The impact of this type of interaction is difficult to quantitate or document, but is seen as an important role of the MMPCs. A third educational mechanism is the publication of ‘how-to’ papers by experts at MMPCs on the design and interpretation of studies with state-of-the-art techniques for metabolic measurements. It would be nice to see even more of this type of information dissemination in the future.

Weaknesses: Any weaknesses in the operation of the MMPCs stem largely from the daunting task of performing rigorous research assays and biological measurements in a highly controlled, yet rapid, manner. This is accomplished in a surprisingly effective manner, considering all of the logistical issues involved. Nevertheless, some areas that could be improved are discussed below.

Lengthy turn-around times for in vivo measurements. An impediment to investigators wishing to obtain measurements performed on live mice (particularly glucose clamps and energy balance studies) is a lengthy waiting period. This is caused by long quarantine periods (6-9 weeks for most centers) and limited capacity for these measurements. A couple of the MMPCs have begun to address the first issue in innovative ways by the use of Flex Air units that eliminate the need for quarantine (Seattle MMPC), or attaining mouse housing and procedure space that is dedicated to MMPC projects (Yale MMPC), which allows performance of some measurements during the quarantine period. The reduction of quarantine time would be a valuable goal at several MMPCs. Solutions for the delays incurred by bottlenecks in performing certain procedures are fairly obvious, and are being tried to various extents at different MMPCs. These include attainment of additional personnel and equipment (e.g., more metabolic cages to increase throughput), offering services that are in demand at multiple centers, and providing training to investigators outside of the MMPCs in performance of key techniques (e.g., glucose clamps). Clearly, these are not trivial issues to address, but in some cases, it might be worth increasing efforts to address them.

Inclusion of highly specialized assays may dilute efforts on heavily requested assays. It is unclear whether the MMPC community benefits from the inclusion of highly specialized assays that will be used by only a handful of individuals, and whether offering such assays dilutes efforts to provide highly requested assays that currently have long wait periods. For example, is it wise to introduce a new hub (such as the Vascular Reactivity Hub at the Seattle MMPC) when there are already insufficient funds to cover personnel needed for the Energy
Balance Core, which is in high demand? The same question could be asked of each MMPC, which often report core services that have 2 users or less per year. While it is exciting from a scientific point of view to offer an in-depth range of services, it is possible that these derail effort and/or funds from other more viable services. The very specialized services could be advertised as possible through collaborative arrangements with specific MMPC investigators, rather than as a service per se. These issues need to be considered on a case-by-case basis.

**Opportunities:**
At present, the involvement of the MMPC program in generating data that is instrumental in research of outside investigators is not transparent, and there is no obvious strategy to improve the reporting by individual investigators of their reliance on MMPCs in their studies. However, it seems that the involvement of specific MMPCs in programs that are familiar to many members of the mouse community should be emphasized. An opportunity exists, for example, in the interaction between the Seattle MMPC and the AMDCC to set the standard for this type of interaction, by publishing methods papers that define benchmarks for analyses, and in reporting the data in a widely accessible way. At present, there is no information about how this interaction will be realized to greatest potential. How many AMDCC strains have been analyzed at Seattle so far? How many are planned? How are the data generated used by the AMDCC; are they disseminated in databases? In publications?

The MMPCs currently fund grants for Pilot & Feasibility studies and for MicroMouse projects. These projects appear to address relevant topics for MMPC personnel, as well as for the larger research community. It would be useful to make available, at least to MMPC personnel, the findings presented in the progress reports from these studies. Certainly, MMPC personnel should be made aware of publications resulting from these studies, although these will likely occur beyond the lifetime of the grants themselves.
VIII. Potential NIH Partners

The MMPC is currently sponsored by NIDDK and NHLBI. New NIH partners could be solicited, which would likely involve the addition of cores or tests to meet new needs. Potential partners include the National Institute of Aging (NIA) and the National Institute of Child Health and Development (NICHD), which have major interests in obesity and diabetes at either end of the lifespan and in maternal/fetal interactions. The National Institute of Allergies and Infectious Disease (NIAID) is interested in the etiology of immune disorders such as type 1 diabetes. NINDS and NIDA are both interested in the control of eating and other health related behaviors that overlap with current and potential future interests of the MMPCs.
IX. List of Appendices

A. 2004 Evaluation by External Advisors

B. Minutes of the Fall 2008 National Steering Committee Meeting

C. Center ‘Criteria for Success’

D. User Satisfaction Survey Results

E. Johns Hopkins School of Business Evaluation and Strategic Planning Report

F. Center Business Plan Surveys

G. Course Student Evaluations
   1. Isotopic Tracers 2007
   2. Isotopic Tracers 2009
   3. Clamping the Conscious Mouse 2004-2008

H. 2009 MMPC Brochure

I. Catalog of Services
Appendix A

September, 2004 Evaluation by External Advisors
Overall the advisors feel that the MMPC serves a significant component of the “mouse community” and that the progress in refining studies for mouse applications is particularly effective. However, there were a number of specific criticisms, as follows:

1. Characterization of obesity in mice should be improved. The difficulty of analysis of feeding behaviors was acknowledged, but the advisors felt that measurement of metabolic rate under isothermal conditions or the availability of yoked-pair feeding capacity should be explored.

2. There was no consensus regarding whether analysis of complications should be a priority of the MMPC. Although the Advisors understood that at the moment there is some effort devoted to analysis of complications such as nephropathy or retinopathy, they felt that a commitment to assess complications diverted the current group from more generally relevant studies. The advisors were particularly concerned that studies of complications inevitably involve comparison to aged controls which in turn introduces practical problems when transferring fragile mice among centers. This might be an area of opportunity for a Center in the future.

3. Improved “one stop shopping” was suggested. The advisors specifically commented that transfer of mice among centers will only become more difficult and that the MMPC could serve investigators if mice could be referred to one site but the strengths of multiple sites could be offered.

4. Better education of the genetics community in mouse physiology was encouraged. A number of avenues were suggested, including published manuscripts and training courses offered at the larger meetings.

5. Better advertising, particularly to investigators on the west coast, was encouraged strongly.

6. The advisors were concerned that the capacity of the current MMPCs is now at their limit.

7. The current web site and other aspects of MMPC dissemination does not adequately reflect the willingness of centers to collaborate and advise on appropriate studies.

2004 Evaluation Suggestions of the Executive Steering Committee
The external advisors met with the Steering Committee to suggest areas for improvement. The executive steering committee agreed that there was a need to advertise the MMPC to a wider community, especially the west coast of the US. We could do another postcard mailing, although it was thought that this would have relatively low impact. It was suggested that members write letters to editors of appropriate journals, such as the diabetes, metabolism and
endocrinology journals, and also to the genetics and animal models journals. We might also put the MMPC website URL into appropriate RFAs as a resource.

The fee structures across the MMPCs are not uniform, and this was a cause for concern. Although we are working toward a more uniform policy about chargebacks and prices, it is complicated by two things: the Universities have different requirements for indirect cost recovery, and some of the tests lend themselves to collaboration (which is not charged) but require much more Center personnel input than a standard fee for service. Therefore, we will continue to work toward a standard policy as an ideal goal, but there is understanding that this cannot be easily accomplished in all cases.

The protocols for all tests must be documented more completely. Although brief protocols for all tests are posted on the websites and in the catalog, there is a need for more detail in the case of some of the more sophisticated tests, especially those that have no well-accepted standard protocol among the research community. This can be tackled by publishing papers, authored by the MMPC consortium, that detail the protocols of the more widely used tests.

Many of the cores in all four MMPCs are currently at or very near their capacity. Efforts should be made to understand the ideal capacity for each core and make sure each operates near that ideal. This is an indication of the success of this project, but must not limit future success and progress.

Immediate Opportunities
There are great opportunities that can be pursued immediately to strengthen the MMPCs and the benefit they bring to the mouse researcher community. The Executive Steering Committee identified these opportunities in two areas: ability to provide ‘bang for the buck’ to investigators that come to the MMPCs for phenotyping, and new ways to educate and train the community, in order to improve metabolic and physiologic phenotyping in general.

It was felt that the MMPCs could utilize animals more efficiently, and collaborate among Centers, in order to do more tests. This could be accomplished in a variety of ways. One suggestion is to administer tracer at the end of the planned set of in vivo phenotyping studies, then freeze plasma and tissues for shipment to the UTSW Center, for NMR isotopic analysis of metabolic pathways. Another suggestion was to freeze the carcasses after sacrifice, and send them to the Cincinnati MMPC for carcass composition analysis. In addition, it was felt that there was a need for a pre-determined “one stop shop” set of phenotyping tests for certain animal models, particularly obese mice. There might be a multi-tiered set of these exams; if a strain shows a particularly interesting phenotype on the first, least sophisticated tier of tests, the MMPC core administrator would recommend to the investigator that it be put through tier 2 in order to more deeply understand its phenotype. These might be described in flow charts or ‘decision trees’ on the web site to help guide submitting investigators as they plan for the appropriate tests.

There is a clear opportunity for the MMPCs to educate investigators in the diabetes and obesity fields regarding metabolic and physiologic phenotyping. This could be accomplished through a set of activities. First, training courses could be set up at the MMPCs to teach
investigators how to do some of the more sophisticated tests. These include clamp studies and NMR isotopic analysis. Vanderbilt is currently piloting a week-long training course for clamp studies, and is very encouraged by their experience to date. Secondly, a symposium for investigators that have used the MMPCs could be organized in order to share their experiences and explore the results of phenotyping across a large number of mouse models using the same set of tests. This would also give the MMPC an opportunity to describe the tests and protocols in deeper detail than would ordinarily be possible, and understand the particular strengths of different tests for models of different diseases. Finally, it was recommended that the MMPC publish a series of manuscripts aimed at standardizing common phenotyping tests and describing the important details and the types of information provided. For instance, the parameters chosen for the insulin clamp experiment (length of fasting, infusion level of insulin, etc.) very much impact the interpretation of the resulting data. Another set of papers could focus on the lessons learned through the process of setting up all the phenotyping tests. For example, the length of fasting can impact on the measured core temperature, can alter weight dramatically, can alter metabolic rate, and insulin resistance. Another example might be diet, where high fat or high carbohydrate diets can be used to uncover interesting phenotypes that are otherwise masked.
Appendix B

Minutes of the 8th Annual
Mouse Metabolic Phenotyping Center (MMPC)
National Steering Committee Meeting

September 22 & 23, 2008
University of Washington
Pan Pacific Hotel, Seattle, WA

Hosted by Dr. Renée LeBoeuf

Contents
- Action Items
- Agenda
- Minutes
- Roster of Attendees
- Preparation for 2009 MMPC Evaluation

Additional Documents
- 2006 P&F progress report (Cincinnati) found at https://www.mmpc.org/secure/showDocument.aspx?id=305&docType=Other
- Alpers Seattle MMPC Histopathology Core Poster https://www.mmpc.org/secure/showDocument.aspx?id=319&docType=Other
- Slide presentations can be found at www.mmpc.org in password protected area, URLs listed below.
Action Items

*Improving Services*
1. A list of FAQs for the website for people needing help to plan phenotyping
2. Diagnostic trees for mice with common first order phenotypes should be developed for the web

*Test Standardization*
3. Update protocols on the web to make sure they are accurate and detailed.
4. Develop Standard Operating Procedures (SOPs) for analyte measurement.
5. Convene small working groups for standardization of other tests/test categories. Center directors should convene to select tests that would benefit from standardization. Identify similar tests among the Centers (the website test catalogue is set up to do this easily on the fly).
6. Explore relationship with other phenotyping efforts (JAX and Europe).
7. Develop a standard mouse plasma sample for use in calibrating tests among Centers.
8. The MMPC should write papers together focused on specific tests—standard protocols when possible, and frank discussion of parameters that affect outcomes in different models/experiments/diets, etc. when necessary. We should establish a relationship with 3-4 high profile journals and initiate an ongoing dialogue with the diabetes/obesity research community regarding best practices for metabolic phenotyping tests in mice. Owen has a draft of a paper that can be the starting point. Important topics: Glucose metabolism and Energy Balance.

*Financial/Business*
9. Compare prices across Centers for similar tests. A small committee should be convened to discuss standardized approaches to developing costs. When extensive protocol development/experimental design is required, this could possibly be considered as a ‘test’ with a flat charge associated with it.
10. Costs should be clearly posted on the websites.
11. Do a market analysis
12. Approach other institutes to see if there would be interest in joining MMPC, and common goals
13. Solicit help with evaluating our business models, including pricing. Suggestions are to employ a consultant or approach a business school to be a Master’s thesis or class project.
14. Advertise more aggressively at meetings (see Charlie Alper’s poster at [https://www.mmpc.org/secure/showDocument.aspx?id=319&docType=Other](https://www.mmpc.org/secure/showDocument.aspx?id=319&docType=Other)).

*Database*
15. Synonyms for test names/test categories should be developed to easily query for data from all closely related tests
16. We should standardize data names among tests and Centers.
17. Database subcommittee needs to be reconvened to help with user interface development

*Evaluation*
18. Collect and post on website ‘stories of success’ on the website, including those of young faculty whose careers were aided by MMPC, successful science
(especially translational), lists of drug targets investigated, etc..

19. Get a survey on line and circulate to past users.

20. Essay on our role in describing metabolic and physiological function, improved technology in the post-genomic era (paper? Web?)

21. Maren and Cristina will draw up an evaluation plan and get started.

Education

22. Plan isotope/kinetics course and hands-on courses. Bob Wolfe and Henri Brunengraber should work on the 2009 lecture course. Assemble a sub-committee to plan hands-on courses, etc.

AMDCC

23. MMPC would like a list from AMDCC of current AMDCC models stored or being made at JAX, and a list of needed markers.

24. MMPC should consider whether complications biomarkers could be analyzed at a single MMPC lab to reduce variability and make it easier to compare AMDCC animal models.

Funding Programs

25. Post solicitation on website for MicroMouse projects for
   a. specific test standardization
   b. database mining
   c. (from Judy Fradkin, NIDDK) mouse models for understanding the role of bariatric surgery in diabetes resolution
AGENDA and MINUTES

MMPC National Steering Committee Meeting
University of Washington
Seattle, WA
September 22 & 23, 2008

Sunday, September 21
Arrive at the Pan Pacific Hotel (taxi from airport)

Monday, September 22
7:30am – 8:00am Breakfast at Lakefront Room
Pan Pacific Hotel

8:00am – 8:15am Welcome
Dr. Renée LeBoeuf

8:15am – 11:00am Brainstorming our MMPC program

8:15am – 9:00am Technology issues
Justification of current methods across MMPCs, updating methods on the web, writing a methods document
Dr. Owen McGuinness
Presentation: https://www.mmpc.org/secure/showDocument.aspx?id=307&docType=Other
Notes: Technology Issues

9:00am – 9:45am Science issues
MMPC course updates & ideas for new courses, education as a mission for the MMPC, setting gold standards for the fields of obesity/diabetes/diabetic complications
Dr. Henri Brunengraber
Presentation: https://www.mmpc.org/secure/showDocument.aspx?id=309&docType=Other
Notes: ScienceIssues

9:45am – 10:05am Speaker: Lung Disease Phenotyping
Dr. William (Bill) Parks
Presentation: lungdisease

10:05am – 10:15am Break

10:15am – 11:00am Business issues: Consistency and transparency in costs
Dr. Colleen Croniger
Of services, specialization of tests to specific MMPCs
Presentation: https://www.mmpc.org/secure/showDocument.aspx?id=310&docType=Other
Notes: BusinessIssues

11:00am – 11:30am Data Base Discussions: data mining & AMDCC data base Dr. Rick McIndoe
Presentation: Notes: Database

11:30am – 12:00pm Walk/Transit by trolley to South Lake Union (SLU) campus
12:00pm – 1:00pm Lunch Buffet (at SLU campus-Admin Bldg C, Room 123)
1:00pm – 1:45pm TOUR CORE FACILITIES (3 groups rotate through 3 core presentations) Dr. Kevin O’Brien
Dr. Charles Alpers
Presentations: https://www.mmpc.org/secure/showDocument.aspx?id=312&docType=Other
https://www.mmpc.org/secure/showDocument.aspx?id=313&docType=Other

1:45pm – 2:00pm Break (coffee, cookies), SLU Brotman Auditorium
2:00pm – 3:00pm SEMINAR: “Mouse model of diabetic complications” Dr. Karin Bornfeldt
Presentation:

3:00pm – 3:15pm Break, return to SLU Brotman Auditorium
3:15pm – 3:45pm AMDCC: Overview & Issues Dr. Frank (Chip) Brosius
Presentation: https://www.mmpc.org/secure/showDocument.aspx?id=311&docType=Other
Notes: AMDCC

3:45pm – 4:10pm Update & Discussion of MicroMouse Grant program Dr. Shawn Burgess
Presentation: https://www.mmpc.org/secure/showDocument.aspx?id=314&docType=Other
Notes: MicroMouse

4:10pm – 4:30pm P & F Report Dr. Elina Minami
Presentation: https://www.mmpc.org/secure/showDocument.aspx?id=315&docType=Other

4:30pm – 5:00pm Walk/Trolley back to Hotel
5:30pm  Wine social at Foyer of Cascade Room  
Pan Pacific Hotel  
6:00pm  Dinner at Cascade Room  
Pan Pacific Hotel  

Tuesday, September 22  
7:30am – 8:00am  Breakfast at Lakefront Room  
Pan Pacific Hotel  
8:00am – 8:30am  Pilot and Feasibility Program Application Review  
Dr. Maren Laughlin  
Notes: PandF  
8:30am – 9:30am  Panel:  Energy Balance  
Dr. Gregory Morton  
Dr. Mike Schwartz  
Dr. Karl Kaiyala  
[https://www.mmpc.org/secure/showDocument.aspx?id=317&docType=Other](https://www.mmpc.org/secure/showDocument.aspx?id=317&docType=Other) (Kaiyala)  
Notes: Panel1  
9:30am – 10:30 am  Panel:  Metabolic Clamping and relationship to IP or oral glucose tolerance testing and IP insulin tolerance testing  
Dr. Julio Ayala  
Dr. Varman Samuel  
Dr. Gregory Morton  
Presentation: [https://www.mmpc.org/secure/showDocument.aspx?id=304&docType=Other](https://www.mmpc.org/secure/showDocument.aspx?id=304&docType=Other)  
Notes: Panel2  
10:30am – 11:30am  Discussion of 2009 MMPC Evaluation  
Dr. Joe Nadeau  
Notes: Evaluation  
11:30am – 12:30pm  Lunch, taxis
Minutes
Monday, September 22
Welcome LeBoeuf Dr. Renée
Dr. John
Slattery
Brainstorming our MMPC program
Technology issues see presentation at https://www.mmpc.org/secure/showDocument.aspx?id=307&docType=Other Dr. Owen McGuinness

How much redundancy of tests among Centers is necessary?
The question was asked whether we should use a single central lab to reduced variability and redundancy, but it was felt that there is value in having several Centers able to measure a variety of analytes. For more complex tests, it was felt that even if some tests were redundant with another Center, it is too hard to ship one mouse model to several different Centers for phenotyping if this can be avoided. Furthermore, there is some sense in having the same test in more than one region. On the other hand, it is really too expensive for all Centers to do all tests, especially complex tests. Centers should specialize. It might be that Centers could share tissue samples among each other after sacrifice to increase the utility from each mouse.

Do we standardize cost and procedures among Centers for similar tests?
Tests that can be standardized include:
- Hormones
- Lipids: TG, FFA (Cinn, VU, Wash)
- Substrate enrichment (Cinn., Yale, UTSW)
- GTT, ITT (VU, Cinn., Wash.)
- Clamps (VU, CW, Yale)
- Energy balance (Wash, VU, Cinn., Yale)
- BP and echocardiography (VU, Wash, Cinn.)
- Morphology (Cinn, Wash, VU)

If we were to standardize common tests, how would we choose parameters that currently differ among Centers? There was concern that we’d have to go to the lowest common denominators, in effect reduce the quality achieved through experience in a given Center. One suggestion was to always include reference strain animals such as male C57/Bl6 mice, which would give an impression of reproducibility over time for a given test, and provide QC for those tests, such as analyte determination, that don’t have standardized QC protocols.

We discussed the idea of circulating test samples to compare analyte measurements among Centers.

NIH Roadmap and NIST have generated a highly characterized standardized human plasma sample for labs developing metabolomics methodologies; it might be possible to do this form mouse (rat?) plasma. It was felt that we should at least standardize analyte tests if possible. If resources are needed, we do have the MicroMouse program and people are encouraged to apply if needed. We should convene a small working group to discuss standardization of tests and come up with a reasonable set of tests and timetable to accomplish this.

Regarding prices, we should share the prices among Centers and compare them…it may not be possible to set them exactly alike for similar tests due to overhead rules, etc., but an attempt should be made to compare them.
How do we document procedures?
- MMPC web site
- Consensus paper?

We could do a better job of describing tests and communicating to the research community, we do have a mission to educate people, and this might include simple things such as ‘what is a high fat diet?’ We should provide definitions and good information about phenotyping mouse models of metabolic disease. We should link to background information at the Mouse Phenome and Mouse Genome databases whenever possible from our database. It was strongly felt that the MMPC should be publishing papers together about standardized tests. We can start with a draft that the Vanderbilt faculty have written regarding carbohydrate metabolism. Owen will share this with other Centers. (Maren’s note: The International Mouse Phenotyping Consortium (IMPC) is being organized by JAX, and is largely a group of geneticists and mutagenesis experts. They are interested in a standardized set of high throughput phenotyping tests to screen for multiple disorders in all biological systems, and an organized system by which large numbers of mice are phenotyped. They have had one meeting so far, and their next is November in Toronto. NIDDK is sending a representative who can report to MMPC).

What is the process we use to make and communicate changes in standardized methods over time?

Protocols tend to be described too briefly in published papers for the reader to fully interpret data or reproduce the experiment, and protocols change both with experience with a given technology and with accumulating knowledge of the biological system. Furthermore, the parameters chosen for one model or expected outcome may be inappropriate for another model with a very different expected outcome. For instance, if glucose dose for a glucose tolerance test is adjusted for total weight of an animal, it may result in elevated glucose and apparent insulin resistance for obese mice relative to lean controls since the fat will take up less glucose than lean tissues. Temperature may affect some animal models more than others. Diet, light/dark cycles can make a difference to test outcomes, and it is clear that the same test in the hands of different people can provide different answers.

MMPC should both make sure that the protocols on the web are highly detailed, and that as changes are made, these are explicitly documented in the posted protocols and/or in the metadata stored with experimental data in the database. Tools can be developed to help in this—forms that can be easily filled out for each experiment with the data that should be included in the database, for instance.

With regard to publishing papers about technology, perhaps an ongoing relationship with journals can be developed so that a series of papers can be published. Blogs and other web-based communication strategies like Wikis were discussed but elicited little enthusiasm.

Suggestions/Issues:
Should our mission be updated to include test standardization?
How much redundancy of tests among Centers is appropriate?
Publication of tests—standards, validation, effects of parameter choices, etc.

Action Items:
26. Update protocols on the web to make sure they are accurate and detailed.
27. Develop Standard Operating Procedures (SOPs) for analyte measurement.
28. Compare prices across Centers for similar tests.
29. Develop a standard mouse plasma sample for use in calibrating tests among Centers
30. Convene small working groups for standardization of other tests/test
categories. Center directors should convene to select tests that would benefit from standardization.

31. Rick McIndoe can provide a grid of tests vs. Centers to easily identify similar tests among the Centers (the website test catalogue is set up to do this easily on the fly).

32. Synonyms for test names/test categories can be used in the database in order to easily query for data from all closely related tests.

33. The MMPC should write papers together focused on specific tests—standard protocols when possible, and frank discussion of parameters that affect outcomes in different models/experiments/diets, etc. when necessary. We should establish a relationship with 3-4 high profile journals and initiate an ongoing dialogue with the diabetes/obesity research community regarding best practices for metabolic phenotyping tests in mice. Owen has a draft of a paper that can be the starting point.

Science issues: MMPC course updates & ideas for new courses, education as a mission for the MMPC, setting gold standards for the fields of obesity/diabetes/diabetic complications.

See presentation: https://www.mmpc.org/secure/showDocument.aspx?id=309&docType=Other

There is a need to fill the vacuum resulting from > 25 years of neglecting metabolic research, with dire consequences for the study of metabolic diseases.

Education is an important goal of the MMPC

Mission of MMPC Consortium is wide, and not limited to fee for service. Includes training users to

– Design protocols
– run experiments
– conduct assays

It is clear that all MMPCs are spending a lot of time in consultation with users, often leading to the ability of the user to do more experiments, design better experiments, etc., and very little of that time is currently billed for. I.e., education and consulting services are an important part of the MMPC mission but do not result in income or MMPC publications. At this point it might be good to find ways to share the lessons learned in these consultations with other users, especially new users. A list of FAQs on the website might be useful, as well as diagnostic trees for mice with common first order phenotypes.

The MMPCs create ‘local energy’ that benefits many people at the institution through conversation and education, as well as its staff. One idea is the use of ‘gatekeepers’ who work with users and record time spent with users (model used by other Centers). Another suggestion is to document ‘stories of success’ on the website—careers started, P&Fs that led to grants or popular papers, lessons learned about animals, new useful tests, etc.

Benefits to MMPC personnel careers

An important consideration is how to ensure that the Universities value the services rendered by MMPC staff. This is especially important for younger PIs who are working toward tenure. Although an independent research program is necessary for tenure, the service elements
and collaborative papers written under the auspices of the MMPC can be helpful. Young faculty benefit from getting some of their salary as they work toward independence, and they can more easily develop relationships with researchers outside their universities, and therefore get a wider reputation earlier in their careers than otherwise. They do have to guard against letting the MMPC soak up all their energy. Some of the Centers feel that their chairs and deans are very supportive of the involvement of young faculty in the MMPC. The rules constraining authorship on MMPC projects with outside users is vexing to young faculty. We might revisit rules on collaborations to take young careers into account. Also, all the credit for the Center grant goes to the PI. There might be a better mechanism whereby the core directors get credit for their portion of the grant (the P01 model? There is a new mechanism used by the roadmap, called ‘linked’ awards. Craig and Shawn have such a grant as part of a Interdisciplinary Research Consortium grant, and it uses the mechanisms ‘RL1’ for research components and ‘PL1’ for cores, each of which has a different PI). Some Centers use a mentorship model, whereby each core has a senior director and a junior director, which provides a support team for both.

Expanding the scope of user protocols
Evolution of the MMPC—should more institutes be included, which would mean expanding both the size of the MMPC program and its mission? For instance, NCI? It was felt that this would be a good idea, if the needs and goals of additional institutes meshed well with those of the existing MMPC.

Developing new assays for users
There is a lot of this going on—Cincinnati is exploring the use of telemetry for long term experiments. Case is developing new deuterated water and other metabolomics assays as they explore user’s needs. Most Centers have or are developing new tests in response to interesting mouse models or ideas brought to them by outside users. In some cases resources are needed for this beyond that budgeted in the MMPC grants—P&Fs or MicroMouse may be of use here. These programs are being used but are certainly not over-utilized at this point.

Education: courses, workshops
– In planning: The MMPC course on isotopic techniques came from brainstorming at 12/2006 MMPC meeting. The first course took place in the fall of 2007, and had 85 participants and 14 faculty. There was ample interaction between teachers and students. A new R25 will be funded 12/2008 for 5 years. The next course will be held on May 3-8 in Little Rock (Bob Wolfe). In addition, a hands-on workshops will be given about once each year under the same grant.
– Needed: There is a need identified to teach GI surgery in small animals, which would be done at the Cincinnati MMPC. This would include lymph duct cannulation and an in-depth look at the special post-operative care required for GI surgery and the appropriate way to do ‘sham’ surgeries as controls.
– Needed: Two-week summer course in Nashville for people who know very little about animals—junior faculty, senior postdocs. This course would help prepare people who have been well-trained in molecular biology and genetics but feel the need to move into functional studies in whole animals.
– Needed: lung biology/emphysema testing in mice (U Washington)
– Needed: mass spec methods (Case), MR isotopomer analysis (UTSW)
– Others...?
Action items:

1. A list of FAQs for the website for people needing help to plan phenotyping
2. Diagnostic trees for mice with common first order phenotypes should be developed for the web
3. Collect and document ‘stories of success’ on the website, including those of young faculty whose careers were aided by MMPC.
4. Plan isotope/kinetics course and hands-on courses. Bob Wolfe and Henri Brunengraber should work on the 2009 lecture course. Assemble a subcommittee to plan hands-on courses, etc.
5. Approach other institutes to see if there would be interest in joining MMPC, and common goals

Speaker: Lung Disease Phenotyping
(Bill) Parks
Presentation:
Should lung phenotyping (physiology, fluid analysis, histology) be added to the MMPC? This is based on the observation that many genetic manipulations are accompanied by ‘emphysema’, probably as a developmental defect. (Cystic fibrosis is within DK’s interests, sleep apnea associated with obesity and lung biology are within NHLBI’s). Lung may also be a very good biomarker tissue for remodeling.

Business issues
Dr. Colleen Croniger
Presentation: https://www.mmpc.org/secure/showDocument.aspx?id=310&docType=Other

How does each center decide on costs?
This is somewhat variable. Some go through a detailed cost analysis of each service, add the overhead costs, and charge a strict percentage of this. Even this careful analysis has limitations; for instance, the capacity of a technician or piece of equipment can be limiting, but if operating at well below capacity, the cost for each given test is higher than it could be. If operating beyond capacity, the cost for adding additional equipment or technicians has to be considered. Should equipment depreciation be figured into test price? The approach should be somewhat uniform across Centers, even if the actual cost cannot be uniform due to different University rules. Should there be cost leaders to supplement cost losers at each Center...increase the price of a few popular tests so that other more expensive ones can be kept a bit cheaper? This seems a good idea to explore. For those experiments where MMPC staff need to spend considerable time developing protocols with users, should there be a flat “protocol development fee”? We would benefit from having a workable business model that spans across all Centers—it should be standardized when possible but flexible enough to accommodate differences at the institutions and among tests. One suggestion might be to enlist the help of a consultant or students and teachers from a business school to give us advise on our business model.

Should we have access to all centers costs? Should costs for services be on website?
In theory, Centers should be able to share the costs of tests with each other, and these should be clearly posted on the websites. It is very difficult to figure out costs from the websites. Part of this is due to the sites not being updated. Part of it is due to the fact that different tests are divided into different types of services—for instance the catheterization can be costed into a clamp or show up as a separate charge on the website. This is considered to be a disadvantage and although it probably cannot be uniform across Centers, the MMPC should look carefully at costs to make sure they are reasonable across the board and in the
same ballpark for similar services at different Centers. The presentation of costs on the web has to be simplified. Having a set of standard SOPs for similar tests would also help this problem.

Should we “specialize” in one or two services and have high throughput to decrease cost? Part of the goal in this discussion is to minimize phone time for Center staff and ‘user shock’ from researchers regarding the bill. It is clear that each Center cannot do ALL tests. But, how much redundancy is optimal between Centers? Issues to keep in mind include the fact that people cannot ship cohorts of mice to several Centers—this is too expensive and time consuming. However, tissues can be collected after experiments and shared among Centers. We could easily be doing more of this. How many sites should do clamps? Indirect calorimetry? Feeding behavior? Cardiovascular workup?

Other ideas—costs for tests really do need to be recouped even if collaborating entities are MMPC staff. Corporate users can be charged more and used to subsidize tests for academics (most MMPCs have a differential charge for industry vs. universities). Yale charges industry 2-3 times what they charge academics.

In advertising, we should provide data showing how much it would cost and how long it would take for an applicant to set up and run specific tests in his/her lab.

**Action items:**
1. **Centers should share fee schedules with each other. A small committee should look into this.**
2. **We need to discuss standardized approaches to developing costs, and this should include the idea that when extensive protocol development/experimental design is required, this could possibly be considered as a ‘test’ with a flat charge associated with it.**
3. **Costs should be clearly posted on the websites.**
4. **We should attempt to do a market analysis**
5. **We should solicit help with evaluating our business models, including pricing. Suggestions are to employ a consultant or approach a business school to be a Master’s thesis or class project.**

**Database Discussions: data mining & AMDCC database**

Dr. Rick McIndoe
See presentation:

Vanderbilt was awarded the first annual “Data Entry” award for entering the most, and most recent, experimental data.

There are still areas where we need to work on the database. We should standardize data names among tests and Centers. We need to collect very complete protocols for all tests. There was discussion regarding those parameters where quantitative data or metadata is needed for a specific test, such as hours of fasting or specific diet. The age range of the animals are required for each test.

The database can accommodate images, such as histology, and these are resident on Rick’s server. There is a nice statistical package, and this can be used for many types of quick data analysis, although it does have limitations, for instance it doesn’t deal with outlying data at this time. Automated messages are in place now for notifying data owners that data
is ready to go public (after 2 years). Users can request an extension of time if they have good reasons for not publishing in the database after 2 years.

Charlie Alpers mentioned that he is making a poster for the U Wash MMPC, and would like to have it posted on the MMPC and NIDDK websites for a couple of weeks. Perhaps other Centers might like to make similar posters to take to conferences and post on appropriate websites.

Next steps: Rick is ready to focus on user interface and usability and will work with the old database committee to do this. He will also work on documentation and training manuals.

**Action Items:**

1. **We should standardize data names among tests and Centers.**
2. **We need to collect very complete protocols for all tests.**
3. **Old database committee needs to be reconvened to help with user interface development**

SEMinar: "Mouse model of diabetic complications"
Dr. Karin Bornfeldt
See presentation:

AMDCC: Overview & Issues
Dr. Frank (Chip) Brosius
See presentation: [https://www.mmpc.org/secure/showDocument.aspx?id=311&docType=Other](https://www.mmpc.org/secure/showDocument.aspx?id=311&docType=Other)

The MMPC would like the list of current AMDCC models stored and being made at JAX. At this point, preliminary phenotyping is being done at JAX as the models are developed, and Eva Feldman will do neuropathy phenotyping if that is desired. Tissues are being sent to U Washington for histopathology. There was discussion of the variability of some test outcomes. Creatinine and albumin were used as examples where high variability is a problem, and GFR/renal function was sited as an example of a needed, useful test (is this still done at Vanderbilt?). MMPC would like a list from AMDCC of needed markers, and will consider whether some of these could be analyzed at a single MMPC lab to reduce variability and make it easier to compare AMDCC animal models. During discussion, the idea came up of AMDCC and MMPC writing reviews and position papers together.

**Action item:**

1. **MMPC would like a list from AMDCC of current AMDCC models stored or being made at JAX, and a list of needed markers.**
2. **MMPC should consider whether complications biomarkers could be analyzed at a single MMPC lab to reduce variability and make it easier to compare AMDCC animal models.**

Update & Discussion of MicroMouse Grant program
Dr. Shawn Burgess
See presentation at [https://www.mmpc.org/secure/showDocument.aspx?id=314&docType=Other](https://www.mmpc.org/secure/showDocument.aspx?id=314&docType=Other)

**Synopsis of applications**
Spring 2008: 2 applications, 1 awarded
• Increased risk for diabetes and obesity in offspring of multiparous mice (PI: Laura A. Woollett, University of Cincinnati)

Summer 2008: 2 applications, 1 awarded
• Effect of murine norovirus on the phenotype of LDL Receptor-Deficient mice (PI: Lillian Maggio-Price, University of Washington)

Fall 2008: 1 application, under review (note: an additional application was moved from the 2008 P&F competition to the Fall 2008 MicroMouse competition).

It is anticipated that there will be 3-4 funded projects in 2008, and for 2009 we should be able to fund 6 projects total, which would allow for 4 new projects and 2 renewals of 2008 projects needing a second year. It appears that the program is working well, and review and funding decisions have been fairly straightforward. Rick has designed a very nice web-based module for application submission, review, voting for funding decisions and communication with applicants. Fewer than 100% of executive committee members have voted on the funding decisions, so this could be improved. Shawn should be commended for his leadership in this program.

We discussed whether there should be a targeted solicitation during FY2009. Suggestions on the table are test standardization among MMPCs and database mining.

**Action item:**

1. **Post solicitation on website for MicroMouse projects for**
   - specific test standardization
   - database mining
   - *(from Judy Fradkin, NIDDK)* mouse models for understanding the role of bariatric surgery in diabetes resolution

P&F Report: Cardiac function in diabetic mice using 2D strain imaging
Dr. Elina Minami
See presentation at [https://www.mmpc.org/secure/showDocument.aspx?id=315&docType=Other](https://www.mmpc.org/secure/showDocument.aspx?id=315&docType=Other)

Pilot and Feasibility Program Application Review
Dr. Maren Laughlin
Progress reports are not yet in from the 2007 P&F awards, but we do have progress reports from 2006 supplements. Two of these (Vanderbilt, Cincinnati) are included as appendices. University of Washington will use 2006 funds to expand the capacity in metabolic cages for energy balance, feeding behavior and activity. This expansion was on hold until the new space was completed and the energy balance lab moved.

Eight 2008 applications were discussed among Center staff personnel and advisors, after Center staff from the competing institutions were excused. After discussion of the scores, strengths and weaknesses of the research plans, and the ‘added value’ of each project to the MMPCs, the advisors selected 3 2008 P&F applications for payment. The PIs will be notified and subcontracts set in place to fund the projects.

08MCG24 Sean Davidson Proteomic analysis of mouse plasma lipoprotein
Panel 1: Energy Balance
See presentation at
https://www.mmpc.org/secure/showDocument.aspx?id=316&docType=Other

Dr. Gregory Morton
See presentation at
https://www.mmpc.org/secure/showDocument.aspx?id=317&docType=Other

Dr. Karl Kayala

Drs. Morton, Kayala and Schwartz led a discussion about issues in measuring energy balance in mice. Elements of the measurement are energy intake and energy expenditure (resting metabolic rate, thermic effect of exercise, dietary thermogenesis). A discussion ensued of technical issues (avoiding animal stress due to housing situation, variation due to access issues to food as a function of animal size, etc., temperature as variable) and interpretation issues (correct way to express data—per animal, per g lean tissue, per g total body weight). It was demonstrated that ob/ob animals appear to have the same, elevated or reduced energy expenditure depending on which normalization scheme is selected. Various systems are used at the MMPCs to measure energy balance (indirect calorimetry with Oxymax (CLAMS) and TSE Systems, or double-labeled water). Karl Kayala discussed a novel statistical (ANOVA) approach to normalization of energy balance data based on the assumption that different tissues (Adipose? Viscera? Liver?) contribute differentially to energy expenditure, and developed by analyzing a large dataset of calorimetry and body composition data taken in many mouse strains. This is an area of active investigation. The discussion was stopped due to time constraints but should be continued. (MRL note: MMPC advisors may want to participate, for instance because EE outcomes are so clearly model-dependent, Tom Gettys feels there are additional experimental approaches to elucidate differences in energy balance that could be employed to reduce data bias).

Action item:
1. Convene subcommittee to discuss energy balance technology and comparative experiments, possible publications, developing insight regarding normalization of data, etc.

Panel 2: Metabolic Clamping and relationship to IP or oral
Ayala glucose tolerance testing and IP insulin tolerance testing

Dr. Julio Samuel

Dr. Varman
Drs. Ayala, Samuel and Morton led a discussion on the tests focused on glucose and insulin metabolism, namely, metabolic clamping and glucose and insulin tolerance tests. Several issues were introduced, along with recommendations for solutions. The first issue has to do with whether these experiments should have standard protocols across Centers. A second issue is how to present data in a standardized format. The point was made that the MMPC can and maybe should be a leader in best practices for publishing standards for clamp data. If we always present data as a timecourse, perhaps this would encourage others to publish it that way as well. A suggestion was made to write a paper proposing ‘minimal information about clamp experiments’ after the MIAME standards for array data (Minimum Information About a Microarray Experiment). A third issue has to do with how we can best educate and inform users of MMPC Centers regarding the best phenotyping approaches for their animals (when to use a clamp, when a tolerance test is the better choice). How best can we use the web, courses and publications to do this? It was agreed that these issues are an important element of our goals for education and to transfer technology. A subcommittee should be formed to discuss these issues. It was suggested that membership should include Drs. Varman, Ayala, Morton and Obici among others.

Panel Discussion Action items:

1. Form subcommittee(s) for the purpose of continuing these important discussions on standardization of protocols and data presentation. These should include interested advisors.
2. Plan and write MMPC publications in the areas of glucose metabolism testing and energy balance testing. Topics include best practices for difficult tests, understanding different parameters and how to choose parameters for a given mouse model and to best answer the research question posed, and how to best interpret clamp and energy balance data.

Discussion of 2009 MMPC Evaluation

Joe Nadeau

The MMPC prepared for this wide-ranging discussion of a 2009 evaluation over the summer. Advisors and Centers were paired, and each advisor looked carefully at his/her assigned Center, either via phone conversations or site visits. These resulted in a framework document.

How to capture the VALUE of the MMPC?

We discussed how to understand and communicate the importance of the MMPC to the nation, and one suggestion was to write and publish an essay on our role in describing metabolic and physiological function in the post-genomic era. This would be an excellent way to advertise the Centers and reach out to potential users. (Even if we only publish on the web, this might be a very useful exercise for the evaluation and provide useful information for DK senior staff and advisory council members).

In the era of genome wide association studies, complex metabolic disorders are still very hard to study and require the use of animal models to even find
candidate disease and modifier genes.

- We need to engage and 'startle' readers, and help people to realize the strengths the MMPC brings to the table: an economy of scale, cost effective, our infrastructure is responsive to and driven by the need for these types of tests.
- Document the cost differential between doing these tests centrally in the MMPC and in individual labs.
- Find and write about success stories from the MMPCS. These would include new ways of treating, diagnosing disease, launching or helping careers of new PIs, new grants awarded based on MMPC data, important new scientific findings.

*Has the MMPC resulted in Improved technology?*

It behooves us to establish gold standards of methods and the MMPC is in a position to do this because of the relatively large number of animals and wide range of models that we phenotype—this gives us the benefit of being able to optimize tests in a pretty efficient manner. Is there a way to estimate whether the MMPC has improved phenotyping of metabolic disease in mice through some sort of continuous interaction with the community ('raising all boats')?

*Consortium Solutions for Common Problems*

One common problem is quarantine. U Washington is working on a technology solution (mobile barrier carts) which might work for some of the MMPCs. Should the next competition of the MMPC include money for this type of equipment meant to solve important common problems?

*Quantitative criteria*

Program income
Publications
# new grants/new applications
Number of new drug targets investigated

*How to capture user opinion?*

Should we consult a random sampling of MMPC users about their experience with the MMPC, or would we need to survey all or most users? What are the elements of such a survey….would we ask them to evaluate data usefulness and quality? Cost? Timing? How do we ensure a robust response to a survey? Should we call some number of non-responders?

*Funding / Income*

Should we pursue other funding agencies and ask them to join the MMPC? This would potentially provide more funds but would also inevitably lead to an expansion of our goals. Potential partners might be NCI (obesity and cancer), NIA (aging), NICHD (development). Maren should start looking into this.

What should our role be vis a vis the pharmaceutical industry? Should we participate in drug discovery or development projects? Is this a way to make money and leverage other services for the academics? Vanderbilt currently charges 1.5 x normal costs for pharmaceutical companies.

*Business Plan*
We should investigate whether MBA students could be engaged to help evaluate our business structure. This would be done of the entire MMPC project rather than a focus on the individual Centers.

There was some discussion about the question of test redundancy among Centers vs. having Centers with very complete sets of tests regardless of those offered at other Centers. We discussed the idea of Centers having tests that are not advertised but are online for local users (clamp at Case?), and Centers that are thinking about reducing the scope of tests offered in order to use those resources to enhance other cores.

Advertising
We need a more aggressive presence at meetings. Charlie Alpers has made a poster to advertise his core at the American Society of Nephrology meeting (https://www.mmipc.org/secure/showDocument.aspx?id=308&docType=Other) and other cores can have similar posters. Cristina Rabadan-Diehl has organized an event at the American Heart Association (URL). We should also advertise in Society newsletters and websites. We might employ the directors of animal cores to disseminate MMPC information to mouse researchers.

Outreach
We should develop a tighter relationship with JAX (phenome database) and other mouse phenotyping efforts (International Mouse Phenotyping Consortium?) and perhaps invite European metabolic phenotype experts to the MMPC. The goal is standardization of approaches to metabolic phenotyping.

Process and Product of Evaluation
Maren and Cristina should write a proposal for MMPC approval regarding the evaluation procedures. They will collect data and write a report. The external MMPC advisors help with advice, will help design the plan, and will evaluate the report and add commentary. The report, once approved by MMPC EAC (directors, core directors, etc and external advisors), will be submitted to senior NIDDK staff and Advisory Council. This will be used in deliberations concerning the next round (years 11-15) of MMPC funding and program.

Action Items:
1. Get a survey on line and circulate to past users.
2. Collect anecdotes of success from Centers to post on web.
3. Essay on our role in describing metabolic and physiological function, improved technology in the post-genomic era (paper? Web?)
4. Maren and Cristina should begin dialogue with other ICs about joining the MMPC
5. We need to advertise more aggressively at meetings.
6. We should explore a tighter relationship with other phenotyping efforts (JAX and Europe).
7. Maren and Cristina will draw up an evaluation plan and get started.
MMPC National Steering Committee Meeting
University of Washington
Seattle, WA
September 22 & 23, 2008

List of Participants

MMPC

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Karin Bornfeldt  Professor, Department of Pathology and Associate Director of the Diabetes and Obesity Center (Speaker), bornf@u.washington.edu
William Parks  Professor of Pulmonary Medicine and Director of the Center for Lung Biology (Speaker), parksw@u.washington.edu
Discussion Framework

Elements to evaluate
- Science, community needs, business plan, administration
- The Evaluation
  - Procedure, product, audience and participants
- The Future
  - Should MMPC change to meet future needs?

Points raised by advisors in response to following questions:
1. What are the overall scientific goals of the Center, are they well served?
2. Is the Center organization and business plan appropriate, and is it working?
3. What are the main scientific achievements and contributions of the MMPC?
4. Is the MMPC serving its scientific community well?

Business Plan and Personnel

Center staff development: While vetting applications for Center use, it is important to protect both the applicant’s needs and the time and effort of the Center staff. Are the Center executive committees engaged where needed to do this? Do Centers choose studies appropriately so that the value of the time spent on MMPC services is maximized? Are Center personnel benefiting appropriately from their MMPC involvement? Some Centers use senior members as mentors to junior members who do day to day service, and this seems to work well.

Advertising: we should do a better job of both reaching a larger group of people so they know about the MMPC, and also communicating the strengths of individual Centers. (cardiac?)

Program income: There should be clear incentives for core staff to produce income. How does a core get to the point where it is working at the right capacity so that income and workload are reasonable and are matched well to demand, yet avoid the state of overuse which would become financially disadventatious? Is there a way to achieve economies of scale, rather than each mouse costing more (this is achieved in some cases)? Is program income being used for new equipment, staff, etc.?

Technology transfer: It was well recognized that many models of teaching and spreading technology are being successfully employed—lecture courses, practical courses, short term one-on-one teaching, seminar series where collaborators are invited to visit and give talks, year long post docs or sabbatical visits. It was also recognized that published test/protocol descriptions must be accurate and detailed.

Scientific Issues

Changing needs, changing science: this point was raised in terms of the need for additional equipment and technicians as cores become popular, and the need for reorganization as cores are shown to be unproductive. Is there a business model that would better and more quickly meet changing needs?

Center scientific focus: some Centers are highly specialized and some broader. Both models are considered good, and Centers can focus resources on highly subscribed cores and
eliminate unused cores where advantageous. In some cases, there are major strengths at the home institution that could be recruited to join the MMPC if a user base exists. (kidney?)

Make best use of mice: Can we coordinate tests better to make better use of each animal/model? For instance, can tissues be saved in one core for use in others or at other Centers? Should we be banking tissues? Can we return tissues to originating lab after experiments are completed?

Expertise as a service: Many MMPC staff spend considerable time consulting with applicants. How can we ensure that the benefits and costs of this are equitably shared? Are MMPC staff benefiting (getting new ideas, promotions, becoming known within study sections, etc., appropriate collaborations). Should this time be charged for? Does the University value this service to others?

Quarantine: Animal care issues can make certain types of experiments difficult or impossible. Is there a solution to the long quarantines that don’t jeopardize animal health and test outcomes?

Core Redundancy, similar tests with different protocols: Should Centers work together to eliminate redundancy and standardize protocols where possible, or is it a better goal for each Center to try to meet as many needs of its client base as possible?

Resources

Database: It is important that MMPC data be made public. We should establish in the near future its main uses, along with its strengths and weaknesses. This would allow us to make changes soon, if necessary. For instance, is there enough metadata to make the test data useful, is it possible to have enough metadata in a database to make it useful? Is data being entered in such a way to ensure accuracy? A problem is that apparently little recent data has been banked, and we need to do a better job. Suggestion: call for P&F to begin mining database.

P&F/Micromouse funding programs: People seem to like these and find them valuable. Can they be improved?

Synopsis of May 28, 2008 planning teleconference—suggested elements in evaluation

a. Metrics: quantitative data is fine to start, but shouldn’t be the whole picture. This includes # and type of test, # of users, # of papers, etc.
b. Science: there should be a focus on areas of science that have been advanced and specific scientific advances due to the MMPC.
c. The whole picture: coordination among the Centers, including the test catalogue and duplicated as well as missing tests, overall business plan, efficiencies realized through the consortium
d. Individual business plans—what works and what doesn’t for the research community and individual MMPC institutions.
d. Programs and benefits that wouldn’t exist without the MMPCs—this is definitely the most important element.

A. Training—mouse clamp course, isotope flux courses, individuals trained at the MMPC labs, etc.

B. Scientific achievements
C. Technical advances, setting standards, careful study of techniques. This could include papers in background strains, papers looking carefully at complex experimental protocols, review papers and consensus papers, etc. Also discussed was the idea of a suggested primary phenotyping list that could be distributed to MMPC users with the idea that the answers would guide future phenotyping, i.e., growth curves, fasting blood glucose, etc.

D. Data analysis –understanding metabolic and technical phenomenon dependent on analyzing data from large groups of animals. An example is how to best normalize calorimetry data for body size or lean body mass.

E. Return on the investment in P&Fs and MICROmouse projects—careers launched, new R01s based on data from these pilot funds, etc. Community building of other sorts includes the phenotyping done for people who wish to gear up themselves to do similar phenotyping in the future, letters written for grants, preliminary data for grant applications, etc.

F. Forward looking, community supporting activities that can be realized through centralized phenotyping. An example might be more thorough understanding of the effects of putative new diabetes genes or genes identified through genomics or GWAS studies.
Appendix C

Criteria for Success
The following criteria were vetted by the MMPC National Steering Committee, and serve as benchmarks of ‘success’ for the Centers and the MMPC program:

1. Number and impact of papers that acknowledge the MMPC;
2. Fraction of papers that acknowledge the MMPC but do not have MMPC personnel as co-authors;
3. Number of Investigators who have used the MMPC and the quality of the resultant research. Number of investigators who have used the MMPC multiple times;
4. Number of users who are not collaborators or Center personnel;
5. Number of tests completed for each core;
6. Capacity of the Center; number of tests that can be accomplished with current resources;
7. Program Income and Institutional Support;
8. Pilot and Feasibility program: number of awards, papers generated under these awards, new tests successfully implemented at the MMPC from these studies, projects successfully funded with independent grants;
9. Completion of Database and population with mouse phenotyping data;
10. Ability to improve and change tests and cores to meet changing needs of research community;
11. Positive feedback from users;
12. Personnel from outside that have been trained by MMPC;
13. Website: maintenance and quality.
Appendix D

National MMPC Customer Satisfaction Assessment

Complete current results found at:
http://www.genomics.mcg.edu/SelectSurveyNET/ResultsOverView.aspx?SID=M83HJ69ZY27NT45

1. Which National MMPC was used for this order of tests?

<table>
<thead>
<tr>
<th>National MMPC</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Western Reserve University</td>
<td>4</td>
<td>6%</td>
</tr>
<tr>
<td>University of Cincinnati Medical Center</td>
<td>13</td>
<td>20%</td>
</tr>
<tr>
<td>University of Texas Southwestern Medical Center</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Vanderbilt University School of Medicine</td>
<td>18</td>
<td>28%</td>
</tr>
<tr>
<td>University of Washington, Seattle</td>
<td>9</td>
<td>14%</td>
</tr>
<tr>
<td>Yale University School of Medicine</td>
<td>20</td>
<td>31%</td>
</tr>
</tbody>
</table>

2. Please tell us your biomedical field of interest?

<table>
<thead>
<tr>
<th>Field of Interest</th>
<th>angiogenesis</th>
<th>glucose homeostasis</th>
<th>molecular genetics and metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>body growth</td>
<td></td>
<td>hypertension and metabolic function</td>
<td>Molecular Nutrition</td>
</tr>
<tr>
<td>Cancer Research</td>
<td></td>
<td>inflammation in obesity and cancer</td>
<td>Nephrology</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td>Insulin Signaling</td>
<td>Neurobiology</td>
</tr>
<tr>
<td>cell regeneration</td>
<td></td>
<td>Liver metabolism</td>
<td>Neurodegeneration</td>
</tr>
<tr>
<td>Developmental and Molecular Biology</td>
<td></td>
<td>liver regeneration</td>
<td>obesity research</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>Metabolic syndrome</td>
<td>osteoimmunology</td>
</tr>
<tr>
<td>diabetes and lipid metabolism</td>
<td></td>
<td>metabolism and genetics</td>
<td>Pediatrics-Nutrition</td>
</tr>
<tr>
<td>diabetes and obesity</td>
<td></td>
<td>metabolism and steatosis</td>
<td>physiology</td>
</tr>
<tr>
<td>Diabetes, muscle physiology</td>
<td></td>
<td>Molecular biology</td>
<td>renal injury and development</td>
</tr>
</tbody>
</table>
3. Please rank your level of expertise in metabolic and physiologic phenotyping on a 7-point scale, with 1 being the lowest level of expertise and 7 being the highest.

<table>
<thead>
<tr>
<th>Expertise Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.12% (2)</td>
<td>6.25% (4)</td>
<td>21.88% (14)</td>
<td>7.81% (5)</td>
<td>20.31% (13)</td>
<td>20.31% (13)</td>
<td>20.31% (13)</td>
<td></td>
</tr>
</tbody>
</table>

4. Please rank your level of agreement with the following statements regarding the Center that completed your order.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center Staff was courteous and helpful.</td>
<td>80.65% (50)</td>
<td>12.9% (8)</td>
<td>4.84% (3)</td>
<td>0% (0)</td>
<td>1.61% (1)</td>
<td>0% (0)</td>
<td>62</td>
</tr>
<tr>
<td>Center Staff was knowledgeable about the tests I ordered.</td>
<td>66.13% (41)</td>
<td>24.19% (15)</td>
<td>4.84% (3)</td>
<td>1.61% (1)</td>
<td>1.61% (1)</td>
<td>1.61% (1)</td>
<td>62</td>
</tr>
<tr>
<td>My tests were completed in a timely fashion.</td>
<td>43.55% (27)</td>
<td>32.26% (20)</td>
<td>11.29% (7)</td>
<td>8.06% (5)</td>
<td>3.23% (2)</td>
<td>1.61% (1)</td>
<td>62</td>
</tr>
<tr>
<td>The tests offered by the MMPC were appropriate for my needs.</td>
<td>64.52% (40)</td>
<td>24.19% (15)</td>
<td>8.06% (5)</td>
<td>0% (0)</td>
<td>1.61% (1)</td>
<td>1.61% (1)</td>
<td>62</td>
</tr>
<tr>
<td>The data I received from the MMPC was in a format that was useful.</td>
<td>64.52% (40)</td>
<td>22.58% (14)</td>
<td>6.45% (4)</td>
<td>0% (0)</td>
<td>3.23% (2)</td>
<td>3.23% (2)</td>
<td>62</td>
</tr>
<tr>
<td>The center staff was helpful in answering any questions about my data.</td>
<td>66.13% (41)</td>
<td>17.74% (11)</td>
<td>4.84% (3)</td>
<td>3.23% (2)</td>
<td>3.23% (2)</td>
<td>4.84% (3)</td>
<td>62</td>
</tr>
<tr>
<td>My overall experience with the MMPC was positive</td>
<td>69.35% (43)</td>
<td>17.74% (11)</td>
<td>6.45% (4)</td>
<td>4.84% (3)</td>
<td>1.61% (1)</td>
<td>0% (0)</td>
<td>62</td>
</tr>
</tbody>
</table>

**Total Respondents**: 62

*(skipped this question)*  2

5. Experience Comments for MMPC

<table>
<thead>
<tr>
<th>Comment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Very helpful. It would be great to be able to get cholesterol profile, but since I was working at a distance, this was not available.</td>
</tr>
<tr>
<td>2</td>
<td>The data obtained through our project with the Vanderbilt MMPC is currently in press and we acknowledged the contributions of the MMPC in this work. Stewart, L.K., Wang, Z., Ribnick, D., Soileau, J.L., Cefalu, W.T., and Gettys, T.W. Failure of dietary quercetin to ameliorate the progression of tissue-specific insulin resistance in C57BL/6J mice weaned onto high fat diets. <em>Diabetologia</em> (in press, accepted 12/3/08).</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>Turned out that the data couldn't be used since the animals were different sizes. I wasn't given any advice about this before the experiment.</td>
</tr>
<tr>
<td>4</td>
<td>The lab had difficulties responding to requests for specific details about kits used for the assays.</td>
</tr>
<tr>
<td>5</td>
<td>The work was done well and resulted in an important publication (Knutson et al., EMBOJ 2008)</td>
</tr>
<tr>
<td>6</td>
<td>I don't view the MMPC's as a service. Every time I've had tests done it ends up being a &quot;collaboration.&quot; If there was truly a fee-for-service, it would be useful.</td>
</tr>
<tr>
<td>7</td>
<td>Several tests I ordered took many weeks to return; communication was poor in the interim regarding the status of the samples.</td>
</tr>
<tr>
<td>8</td>
<td>The Center Staff were receptive to suggestions I had about the samples.</td>
</tr>
<tr>
<td>9</td>
<td>The MMPC is a terrific resource to have available.</td>
</tr>
<tr>
<td>10</td>
<td>Turn around time is too long in general. Some concerns re: inter- and intra-assay variability. Robust internal controls would be helpful.</td>
</tr>
<tr>
<td>11</td>
<td>Assays were completed rather rapidly, but the data wasn't initially sent out due to an error. Data was sent immediately after I called.</td>
</tr>
<tr>
<td>12</td>
<td>As indicated above, they provided a great service for my studies. We could not have done them without them.</td>
</tr>
<tr>
<td>13</td>
<td>Directors (Wasserman and McGuinness) and other MMPC staff were always available to meet and review data, beyond the service provided.</td>
</tr>
</tbody>
</table>
The center need to communicate and inform the user when there is a change of original agreed protocol.

The Seattle MMPC has served as a valuable resource for my research program. The Director (Renee LeBoeuf) has provided very thoughtful insight into assisting concerning the phenotype analysis of our mice.

17. My only concern is the long wait time for the assays to be run. I got the impression that the facility was overwhelmed with samples. We had to wait usually 4-6 weeks. (MMPC lipid core Vanderbilt)

Dr. Le Boeuff and colleagues were extremely helpful to us is all aspects, from study design through interpretation and reporting of the data. We hope to send more work to the MMPC and are seeking funding to do so.

My interaction was attending a training course (Vanderbilt MMPC mouse clamping course). As a clinical academic (assistant professor equivalent) this was probably the single best use of a week of my time in the last 7 years. Thank you to Dave Wasserman and team!!

the schedule for animal phenotyping experiments was quite booked, and it took a long time to schedule these

6. Statements about the MMPC website

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
<th>Response Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>The quality of the content provided on the website is satisfactory.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>(skipped this question)</td>
<td>14.52% (9)</td>
<td>48.39% (30)</td>
<td>20.97% (13)</td>
<td>3.23% (2)</td>
<td>1.61% (1)</td>
<td>11.29% (7)</td>
<td>62</td>
</tr>
<tr>
<td>The website is easy to navigate.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>(skipped this question)</td>
<td>16.13% (10)</td>
<td>35.48% (22)</td>
<td>27.42% (17)</td>
<td>4.84% (3)</td>
<td>4.84% (3)</td>
<td>11.29% (7)</td>
<td>62</td>
</tr>
<tr>
<td>I was able to find the information I needed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>(skipped this question)</td>
<td>16.13% (10)</td>
<td>43.55% (27)</td>
<td>20.97% (13)</td>
<td>4.84% (3)</td>
<td>1.61% (1)</td>
<td>12.9% (8)</td>
<td>62</td>
</tr>
<tr>
<td>Placing an order on the web site was easy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>(skipped this question)</td>
<td>16.13% (10)</td>
<td>27.42% (17)</td>
<td>24.19% (15)</td>
<td>3.23% (2)</td>
<td>3.23% (2)</td>
<td>25.81% (16)</td>
<td>62</td>
</tr>
</tbody>
</table>

Total Respondents 62

7. Experience Comments for MMPC website

1. I haven't used the website, actually. I just checked it now and it seems easy to use.

2. The website could be immensely simplified. It is unnecessarily convoluted.
It was difficult to really understand what types of serum tests they could perform. I had a tough time locating the information online so I contacted Gary Cline directly, and he was extremely helpful and courteous.

Because a login is required, the website should be personalized so that we do not need to key in the same info over and over when we place another order.

The website is difficult to use often needs updating and is confusing regarding availability of tests to individual centers.

Since we go through an ordering group, I cannot comment of the ease or ordering.

Hard to even find the website from UC's home page.

Ordering through MMPC site is confusing. Sometimes tests are listed on the website for individual center but not in the main website where you order the tests.

Did not use this website.

### 8. Problems with animal/tissue handling.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Shipping to the Center</td>
<td>4</td>
</tr>
<tr>
<td>Receiving at the Center</td>
<td>0</td>
</tr>
<tr>
<td>Animal Care and/or sample storage at the Center</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total Respondents** 4

( skipped this question) 60

### 9. Please describe any problems you encountered.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>Instructions were not very detailed. Cages flooded, surly delivery driver wanted elastic bands around cages...pick-up was at 8am. It was tough to have 30 singly caged animals out on a cold loading dock at that time.</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Not all studies are performed at all centers. For instance for Thyroid hormone assays, I had to send to Vanderbilt, and for metabolite</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>No issues</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>I shipped animals to Cincinnati without a problem and after they finished analyzing the mice, they shipped them back to me without a problem.</td>
</tr>
<tr>
<td>9</td>
<td>Time between shipping to Charles River for quarantine and actually studies at the MMPC is too long.</td>
</tr>
<tr>
<td>10</td>
<td>Needed quarantine as mice were returned to VA. Mice were &quot;run&quot; several times before the operator realized they had been on a low-fat diet.</td>
</tr>
<tr>
<td>11</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>No problems</td>
</tr>
</tbody>
</table>

### 10. Did you publish the data?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td><strong>24</strong></td>
</tr>
<tr>
<td>No</td>
<td><strong>8</strong></td>
</tr>
<tr>
<td>Not yet, but I am planning on using it in a publication</td>
<td><strong>34</strong></td>
</tr>
<tr>
<td><strong>Total Respondents</strong></td>
<td><strong>62</strong></td>
</tr>
<tr>
<td>(skipped this question)</td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

### 11. Did use the data for a grant application?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td><strong>31</strong></td>
</tr>
<tr>
<td>No</td>
<td><strong>11</strong></td>
</tr>
<tr>
<td>Not yet, but I am planning on using it in a grant</td>
<td><strong>20</strong></td>
</tr>
<tr>
<td><strong>Total Respondents</strong></td>
<td><strong>62</strong></td>
</tr>
<tr>
<td>(skipped this question)</td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>
Appendix E
Johns Hopkins School of Business Evaluation and Strategic Planning Report

MMPC Business Plan Evaluation and Strategic Planning

Prepared in partial fulfillment of the requirements for the MBA degree in Medical Business Management for the Johns Hopkins School of Business, Spring semester, 2009

Tony Richardson, MBA
Yasmin Abbas, MBA
Abby Lipsitz, MBA
Karen Rothrock-Dixon, MBA
INTRODUCTION

Strategic planning and its evaluation is a process that allows the organization to fully envision its future and construct the required pathways in reaching that future. With the involvement and commitment of all stakeholders, it can be a means to manage change. A successful planning process involves realistic performance measures that assess the progress of the organization. It should be viewed as a means of enhancing and empowering employees by encouraging open and honest discussions that considers the organization as a whole. The strategic planning begins with some very basic questions:

- Where are we?
- Where do we want to be?
- How do we get there?
- How do we measure our progress?

When considering the Mouse Metabolic Phenotyping Centers (MMPC), the objective of this process is to establish the blueprint for the continued life of the MMPC and consortium. It is a means that supports and ensures the sustainability of an organization and or collaboration. The process assesses the culture of the hosting institutions and mission of the funding sponsor in comparison to past, present and future demands. The strategic plan projects the ability of the centers and consortium to maintain current research and support future projects. Although the initial planning may appear to be complex in nature, it is important that it is practical in application. The success of any plan, in part, is measured by its flexibility. The building of the plan takes into account the primary stake holders as well as the subordinate stake holders. In short, this requires the inclusion of each site’s participation and planning in support of the MMPC mission to fuel a common vision. Management and organizational structures are the guiding post for this task. The objective of both is to begin to operate systematically and comprehensively in the direction of this vision. In the changing current environment of research, the management and the organizational structure should channel the strengths of each site individually towards the common vision of the whole as it strives to accomplish the overall mission. While the choreographed picture may seem daunting, through cooperation it can be plausible. In pursuing this endeavor it is important to maintain and use basic terminology that promotes inclusiveness rather than excluding certain disciplines. Since the mission statement has already been formulated, the operational and strategic planning should be even more understandable to the stakeholders. The operational or tactical planning consists of the day to day aspect of a business normally within the time frame of a year, whereas the strategic planning probes further into the future sustainability of the organization. Understanding how each stakeholder contributes to the mission must be clear and open for healthy discussion and stimulates wide spread support for the final decision. The operational and strategic business planning process should weave the vision of the centers into the goals of the mission by complementing each other.

Analysis:

The goal of the Consultant Group was to make recommendations that would bring the varying administrative processes and functions in line with current business goals. In order to deliver the required assessments and analyses the Johns Hopkins Capstone Consulting Group worked
under the direction of the Senior Advisor for Integrative Metabolism, Maren R. Laughlin, Ph.D., and the Johns Hopkins Capstone Consulting Group coach, Roger Orsini, M. D., provided by Johns Hopkins Business School. Considering the size and dynamics of the services provided at each site and the complexity of the NIH and MMPC relationship, the consulting group decided to center the assessment on the areas of marketing, operations, and financial stewardship. In order to establish a cohesive business strategy within this research centered collaboration, the following methods were used:

1. Meet with multiple site directors and other staff to assess administrative processes
2. Interview key stakeholders at a minimum of 3 sites:
   a. Case Western Reserve University
   b. University of Washington, Seattle
   c. Vanderbilt University School of Medicine
3. Analyze market research based on competitive comparable laboratories.
4. Review Annual Business Reports
5. Evaluate current business practices by use of questionnaires for:
   a. Economies of scale
   b. Cost sharing strategies
   c. Pricing Models
   d. Utilization and capacity reporting
   e. Procedures to measure funding compliance

This information was provided by e-mail, fax, phone and/or on-site interviews and incorporated in our use of standard business assessment tools, such as the Strengths, Weaknesses, Opportunities and Threats (SWOT) analysis.

With any strategy or plan, one must begin with the development of a mission. As previously mentioned, in the context of the MMPC the mission has been developed:

To advance medical and biological research by providing the scientific community with standardized, high quality metabolic and physiologic phenotyping services for mouse models of diabetes, diabetic complications, obesity and related disorders.

From this basis, the planning process is born. It is mostly developing a common understanding of the future purposes of the Centers in meeting this mission. The planning process can be simplified if viewed in three different categories. These categories are; operational, tactical and strategic. Most successful enterprises have sound documentation for all three categories. As mention previously, the operational planning describes the day to day operations of a center, core or unit in achieving the overall mission. The tactical plan extends this planning out from day to day to that of year to years. The strategic planning goes a step further by projecting the operational and tactical endeavors into a long range map. There are several tools used by organizations in formulating a strategy.

Analysis of Strengths, Weaknesses, Opportunities and Threats

One of the most common approaches is to develop a SWOT analysis. The SWOT represents the Strengths, Weaknesses, Opportunities and Threats of an organization. The strength and
Implicit in the SWOT analysis is the aim of achieving the optimum match of resources in order to gain a sustainable competitive advantage. More importantly, it offers a view of the strengths and weaknesses in the context of the opportunities and threats. The first step is simply to list the important strengths, weaknesses, opportunities and threats as they are currently perceived by the stakeholders.

(Diagram from: [http://en.wikipedia.org/wiki/SWOT_Analysis](http://en.wikipedia.org/wiki/SWOT_Analysis))

In reaching this objective the above SWOT diagram can be used to flesh out the steps in the planning process. The aim of any SWOT analysis is to identify the key internal and external factors that are important to achieving the objective. These come from within the company's unique value chain. SWOT analysis groups key pieces of information into two main categories:

- **Internal factors** – The strengths and weaknesses internal to the organization.
- **External factors** – The opportunities and threats presented by the external environment to the organization.
The members of the Johns Hopkins Capstone project used the above format in creating a broad SWOT analysis of the MMPC and Consortium:

<table>
<thead>
<tr>
<th>SWOT</th>
<th>WEAKNESSES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STRENGTHS</strong></td>
<td>Internal Competition</td>
</tr>
<tr>
<td>Unique Tests</td>
<td>No communicated vision (short/ long-term)</td>
</tr>
<tr>
<td>Scientific/ Technical Expertise</td>
<td>No marketing budget</td>
</tr>
<tr>
<td>Mission Focused</td>
<td>No consistent Business Plan, Strategic Plan, or Marketing Plan</td>
</tr>
<tr>
<td>NIH affiliation</td>
<td>No Standardization of Pricing, Fees, Operations, etc…</td>
</tr>
<tr>
<td>Credibility</td>
<td>Non-multidisciplinary staffing model</td>
</tr>
<tr>
<td>Collaboration</td>
<td>Unique Tests</td>
</tr>
<tr>
<td>State of the Art Technology</td>
<td>Centralized Database</td>
</tr>
<tr>
<td>Centralized Database</td>
<td><strong>OPPORTUNITIES</strong></td>
</tr>
<tr>
<td><strong>THREATS</strong></td>
<td>Mouse Transfer Protocol</td>
</tr>
<tr>
<td>Education/ Training Endeavors</td>
<td>Centralized Database</td>
</tr>
<tr>
<td>Center of Excellence</td>
<td>New laboratories</td>
</tr>
<tr>
<td>Co-authorship</td>
<td>Competition for Grant Funds</td>
</tr>
<tr>
<td>Collaborations</td>
<td>Overlapping customer base</td>
</tr>
<tr>
<td>Expansion of local customer base</td>
<td>External Competition</td>
</tr>
</tbody>
</table>

The SWOT analysis is not limited to just profit-seeking organizations. It can be a useful tool in any decision-making situation when a there is a defined outcome or objective. It is important to base the SWOT with the mission of the MMPC as the final objective. The following information outlines each segment of the SWOT analysis and briefly describes the reasoning for it’s categorization into that segment.

**STRENGTHS**

- **Unique Tests:** The centers individually and collectively offer laboratory tests that are specific to a specified field of research.
- **Scientific/ Technical Expertise:** The centers are staffed with individuals who have dedicated themselves to the pursuit of research. In doing so they provide an invaluable amount of knowledge.
- **Mission Focused:** Each center has designed cores that specifically relate to the demand and need of the research environment.
- **NIH affiliation:** As described in the mission, “The NIH provides leadership and direction to programs designed to improve the health of the Nation by conducting and supporting research”. In reaching this mission the NIH has established a sound and reliable reputation that is extended to those that are aligned by association.
- **Credibility:** Each center is located within an academic institution that also serves as a beacon of excellence in the pursuit of knowledge.
- **Collaboration:** This is evidenced by the formulation of internal and external committees within the consortium. This can also be seen in the relationships that MMPC personnel have developed with individual outside researchers.
- **State of the art Technology**: The MMPCs are aligned in progressive academic institutions known for their innovations in research.

**WEAKNESSES**
- **Internal Competition**: The format of applying for grant funding is purely competitive in nature. This tendency is often hard to abandon after the awarding period. This should not be completely seen as negative because it does inspire innovation and creativity.
- **No communicated business vision (short/long-term)**: There’s a faulty perception that non-profit organizations are not allowed to make profit, when in fact they should make profit so they can improve and enhance their business development.
- **No Consistent Business Plan, Strategic Plan, or Marketing Plan**: Part of the different pricing policy is the co-authorship arrangement in the different centers. Some centers waive the fee for service in cases of co-authorship which attracts the price sensitive customers to these centers. This may also create a perception of conflict of interest. The preponderance of the evidence is in support of this theory that when there is a vested interest, quality or equality can come into question. No matter how altruistic the intentions, there should be transparency in all endeavors. This may not alleviate all concerns, but does tend to limit them. The absence of a formalized strategic or marketing plan leaves the centers without direction and can possibly hinder the rate of growth.
- **No Standardization of pricing or fees**: Each MMPC center has its own pricing policy, leading to widely varying prices for the same service. This leads to customer confusion and questioning of the standardized quality of test across the different MMPC centers. It is noted that there are local variables that contribute to this practice.
- **Non-multidisciplinary staffing model**: Although the scientific aspects are clearly multidisciplinary, the business end is not. The management and planning of the MMPCs should include those assigned to the business development and sustainability.
- **Unique Tests**: Although this is seen as strength, it is also limited by a predefined market area.
- **Centralized Database**: There are no measures in place that would monitor the consistency in data input nor monitor the compliance.

**OPPORTUNITIES**
- **Education/Training Endeavors**: By providing comprehensive educational opportunities in conjunction with intern/externship, the MMPC can further expand their market areas and establish themselves as educational sites of excellence. The experience gained by students further the sites advertisement area and aligns it strategically with the mission of by providing the scientific community with the tools necessary for research.
- **Center of Excellence**: Each center can develop its unique branding into Centers of Excellence Programs that promote and accelerate promising technologies and test that have strategic value
- **Co-authorship**: When accomplished with established and transparent guidelines, this promotes the work of the MMPC as a whole.
- **Collaborations**: The value of collaboration not only benefits the research specific effort, it also lends efficiency to administrative measures.
- **Expansion of customer base**: The customer base outside of the immediate center location and in partnership with private/public entities. The customer base can be expanded both by
advertising and by continually making sure that the services offered are of high interest to the potential users.

**THREATS**

- **Mouse Transfer Protocol:** Legal constraints (intellectual property) and protocols governing the handling and acceptance of mice (quarantine)
- **New laboratories/ External Competition:** Internal and external laboratories within and outside of the MMPC parent institutions are entering the market.
- **Competition for Grant Funds:** As new universities and laboratories enter the competing market, the competition for funding also increases. Therefore, continued grant support is not guaranteed.
- **Overlapping customer base:** Without a consistent or reliable customer database it is hard to measure the true customer or market base. In short, you can manage only what you can measure.

The current management and organizational structure is without doubt geared towards the mission of supporting science. No matter how admirable the mission, there has to be a plan that aligns the visions of each in accomplishing this mission. The overall impression of the Johns Hopkins Capstone project was that the quality of the work and dedication of the staff is remarkable. The attentiveness of the MMPC practice in producing quality service is important in and keeping customers and thereby providing the foundation for sustainability. However, the diligence and worthy practice of research needs a compass to forecast future demands. It sets the direction of the center (s) and serves as a guide to smaller supporting plans. Without a viable planning structure for the future endeavors it can lead to non-existence in a growing and competitive market.

**The recommended Business Strategy**

Organization and Management require a much more consolidated approach in maintaining sustainable vitality. The real value of developing a business strategy is not the hand held finished product. The true value lies in empowering those involved to have input into the development of a cohesive vision in the achievement of a shared mission. In short, this requires the inclusion of each site’s participation and planning in support of the MMPC mission that fuels a common vision. Management and organizational structures are guiding post for this task. The objective of both is to begin to operate systematically and comprehensively in the direction of this vision. In the changing current environment of research, the organizational structure should channel the strengths of each site individually towards the common vision of the whole.

Based upon the SWOT analysis, site visits and questionnaire surveys, the Johns Hopkins Capstone participants began to draft a recommended business strategy and to focus on those variables that would have a direct impact upon its success. The original guidance established during the previous RFAs was not explicit enough beyond the tactical day to day operations. The individual sites in part have addressed this intent with the formulation of the Administrative Core. Given the nature of research and the constant changing environment of
funding, there is a growing need to actively develop needed parameters for establishing sound business acumen that will ride the waves of change.

**Current Situational Assessment (Based on Surveys and Site Visits):**

- During the interview process with MMPC Center Directors it was assessed that due to the number of steps involved in the request/application process, certain steps are often bypassed for simplicity and expedience purposes. In addition, consulting time spent with investigators about test description and applications prior to testing was not documented or reimbursed through MMPC grant money. It was relayed that a considerable amount of time goes into this part of the process and Center Directors do not currently have a system for capturing time allocated to this function. It was also noted that the workload of each MMPC site is reported cumulatively instead of capturing/reporting out on the workload data for each individual core at the site. Web based tools for administration are in place but are not universally used.
- All of the MMPC’s have a different workforce depending on the nature of the research being conducted at that particular MMPC. The types of employees range from technical to scientific to administrative. The workforce is primarily comprised of professional employees and turnover of this professional staff is relatively low. When a position does become vacant new hires are generally hired through networking and word-of-mouth. The pay structure varies at each facility based on Institutional base salary plus fringe benefits. Each MMPC has their own training policies and procedures and coordinates training as needed within its own individual MMPC site. After reviewing the MMPC survey it was unclear if there was a formal plan for training and succession in most of the centers, or if there was a system for capacity building programs for their staff.
- Each MMPC center has its own pricing policy, leading to widely varying prices for the same service. This leads to customer confusion and questioning of the standardized quality of test across the different MMPC centers.
- Part of the different pricing policy is the co-authorship arrangement in the different centers. Some centers waive the fee for service in case of co-authorship which attracts the price sensitive customers to these centers. We feel that this also creates an imbalance as it may lead to imbalance in the published paper load among centers and also may lead to scientific-bias condition.
- Manpower and salaries constitute the largest portion of the costing process of different tests. Shown below is one of the costing models (per mouse) used in many, but not all, centers:

<table>
<thead>
<tr>
<th></th>
<th>TT</th>
<th>TSR</th>
<th>SRF</th>
<th>Salary</th>
<th>CM</th>
<th>SR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic CA &amp; JV Cath</td>
<td>3</td>
<td>30</td>
<td>0.6</td>
<td>$54.00</td>
<td>$10</td>
<td>0.7</td>
<td>$91.43</td>
</tr>
<tr>
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<td>30</td>
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<td>$36.00</td>
<td>$10</td>
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<td>30</td>
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<td>$54.00</td>
<td>$10</td>
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<td>$36.00</td>
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<td>0.6</td>
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<td>30</td>
<td>0.6</td>
<td>$54.00</td>
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<td>0.8</td>
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<td>0.6</td>
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<td>30</td>
<td>0.6</td>
<td>$9.00</td>
<td>$5</td>
<td>0.9</td>
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Formula: \( \frac{(TT \times TSR \times SRF) + CM}{SR} = \text{PRICE} \)

Legend:
- TT- Tech Time
- TSR- Tech Salary Rate
- SRF- Salary Recovery Rate
- CM- Cost of Material
- SR- Success Rate

- The documents used are not standardized accounting financial forms. They are not self explanatory and hard to read and interpret.
- There’s a faulty perception that non-profit organizations are not allowed to make profit, when in fact they should make profit so they can improve and enhance their business development.

RECOMMENDATIONS:

**Overall Business Strategy**
- To develop a financial sustainability plan
- Develop business outcome measures and targets
- Develop marketing strategy
- Establish a business oriented planning and decision making body or hire a Business Development Specialist to prioritize and implement good business practices

**Human Resources**
- The workforce is primarily comprised of scientific professionals, Center Directors and Center Co-Directors focused on research. Unlike other business models, it is somewhat one-dimensional in this respect. It would be beneficial if a member of the team or a new position be identified to take on a business practice and planning role of the MMPC as it pertains to business development and marketing.
- The establishment of staff development models that address turnover rates and provide documentation of: Career goal assessments, Quality reviews and training (new and ongoing)

**Price Structure**
- To implement the use of Activity Based Costing (ABC) to assist in internal and external benchmarking and identifying costs and savings associated with dissemination of best practice. It will also help by identifying the non-value added activities and eliminating them, hence ensuring revenue efficiency achievement.
- To develop a set of costing and pricing principles designed to fully absorb costs of all MMPC services based upon income performance goals and measures. By doing so, discrepancy between different centers is eliminated and thus customer confusion is eliminated.

**Accounting and Reporting**
• To prepare and issue standardized reporting of accounting/financial statements.
• In addition, workload of each MMPC core is reported cumulatively. This is helpful when obtaining data regarding each MMPC in its totality but it does not give a clear breakout of the performance of individual core businesses in order to assess capacity, utility and profitability. It is recommended that MMPC Cores report data individually as well as cumulatively in order to better identify strengths and weaknesses of each core as it relates to utility of specific testing. In addition, it would provide each MMPC with information to better make data driven decisions as they work to develop, change or maintain specific testing.

**Work Flow**
• Based on the individual MMPC interviews with Core Directors and operational survey questionnaires, similarities between responses are noted relating to workload, personnel and inventory. There are multiple steps involved in the request and application process for the investigator when ordering a test. Investigators may tend to bypass some of the steps for simplicity and expediency. A detailed uniformed workflow and documentation process should be developed in order to identify proper sequencing and any duplication of the process as well as “non-value added steps”. Making better use of the electronic administrative tools could greatly improve this process.

**Client-Center Relations**
• Documentation of staff consultation time and effort. This will help to decide if time spent talking with clients is appropriate and help strategize if it is excessive or ineffective.
• There was ambiguity in use of the term of “Collaboration”. A well defined process or policy that is communicated to its purpose and use would clarify this issue.
• Recommend that scientific collaboration and service fees are kept completely separate and transparent. Members of the collaboration can decide who pays the MMPC fees. Documentation of collaboration agreements should be explicit about occurrences of co-authorship
• Customer base development such as: Newsletters, invitations to symposiums and educational courses

**STRATEGY**

The business aspects of the MMPC could be served either by the formation of a committee, or by hiring a Business Development Specialist.

**Option A: Committee**
Through the creation of a single vision by a management structure that focuses on the financial aspect, the MMPC can continue to do what it does best. This function, in other research and development entities, normally falls under the auspice of a Business Development Unit (BDU). BDU responsibilities are taken on by a subcommittee with representatives for each of the MMPC sites that centrally oversee this task. The key to its success would be standardization of business practices through strategic planning and measurable outcomes in support of the mission and vision of the MMPC. The creation of a permanent, professional, business-oriented, multi-disciplinary national planning body would
bring together all stakeholders to address the challenges that the consortium faces in a comprehensive, coordinated and strategic manner. The true configuration of this body or team would be based on the business strategy of the MMPC sites (Durates, 2000). The proposed activities would include a charter outlining the members, roles, responsibilities, and operations of a consortium wide business development committee. The following are suggested areas of consideration:

- **Goals and Objectives** – The Business Development Unit should establish annual strategic development goals and objectives concurrent with funding trends. These goals and objectives should include existing strategic development efforts, as well as prioritizing new initiatives. In addition to cost and performance goals, any strategic plan must be balanced and in concert with the mission and vision of the MMPC.

- **Performance Measures** – The Business Development Unit would establish consortium-wide performance measures and reporting requirements in order to monitor and continuously improve the strategic development that reflect the needs of the program and with respect to the individual sites.

- **Marketing Strategy to the potential user’s community** – The plan would include a communication strategy that clearly conveys NIH’s commitment to the effort, describes the scope of the effort, and identify any organizational changes. The communications strategy should also include steps to make MMPC sites as a whole aware of research collaborations, educational endeavors, marketing initiatives and strategic plans.

Based upon the questionnaire responses and direct interviews with staff, the following information was abstracted as key elements to be addressed within the concept of a BDU:

**Operations:**
1. Quality Assurance/ Performance Improvement Measures (how do they measure MMPC performance?), Goals/planning (annually)
2. Scientific Gap Analysis (where & what development is needed)
3. Standard co-authorship and collaboration documentation policy
4. Centralization/standardization of administrative issues
5. Business training

**Finance:**
1. Standardized financial documents/reporting
2. Standardized costing model
3. Consultation fees (for Center staff consultant with clients)
4. Documentation of revenue generation & re-investment/ correcting the concept of “not-for-profit”

**Marketing:**
1. Marketing activities/ website and customer base development
2. MMPC training programs (structure, costing, on-line support)
3. Publicizing educational opportunities
The above recommendations are described as the functions of a committee, but could also be accomplished under the consideration of an individual in a centralized business-oriented position, an MMPC Business Development Specialist.

Option B: MMPC Business Development Specialist

Provide recommendations to the Administration and MMPC committees to address pertinent areas of current interest as it pertains to the sustainability and development of the MMPC/Consortium.

Key areas include:

Operations:
1. Quality Assurance/ Performance Improvement Measures (how do they measure MMPC performance?)
2. Standard co-authorship and collaboration policy
3. Centralization of administrative issues
4. Business training

Finance:
1. Standardized financial documents
2. Standardized costing model
3. Consultation fees
4. Revenue generation & re-investment/ correcting the concept of “not-for-profit”

Marketing:
1. Marketing activities/ website development
2. MMPC training programs (structure, costing, on-line support)
3. Publicizing educational opportunities

Position Summary: The MMPC Business Development Specialist is responsible for participating in implementation of the business/ market development plan to ensure maximum alignment with research objectives. The incumbent will also work to increase market penetration of the MMPC and co-promoted services within the MMPC guidelines and according to the governing regulations of NIH. The Business Development Specialist will conduct their business with key targeted researchers who may be associated with federally funded grants/contracts, pharmaceutical and other targeted accounts.

Responsibilities:

- Maintains and utilizes expert sound program knowledge of research/clinical knowledge and highly effective organizational skills in order to influence administrative processes in a research environment.
- Plans business strategies targeted to research professionals to appropriately increase recognition, diagnosis and treatment rates within the MMPC market areas.
- Executes brand strategies to ensure a consistent marketing and planning message that is consistent with the mission of the MMPC.
Establishes and maintains effective communication/cooperation/coordination with the Administrative Directors of the MMPC and the Coordinating Bioinformatics Unit.

Fosters ongoing interaction and partners within the MMPCs in execution of a market development plans and to ensure administrative consistency.

Coordinates and reports to the MMPC leadership customer responses and assessment of services.

Identifies thought leaders, innovators and advocates while working with them to implement business initiatives consistent with the mission of the MMPC.

Provides feedback and follow-up to speakers and attendees. Initiates contacts and network-building among thought leaders and clinicians.

Monitors core MMPC core programs and budgets to stay within standards.

Performs all business, including conducting all promotional activities, in accordance with all applicable federal laws, regulations, policies and procedures. When suspected violations of these requirements are noted or observed, they are immediately reported in good faith in accordance with policy.

Demonstrate high ethical and professional standards with all business contacts in order to maintain the reputation of NIH and the MMPC within the research community.

Overcoming complexities and barriers found in research is a common phenomenon. In a society fueled by the need to accelerate the pace of discovery for new disease treatments, prevention strategies, and diagnostics, overcoming the limitations of one’s knowledge is necessary. The independent silos of discovery have given way to the research team. The dynamics of that team have grown to include a multitude of professionals that do not typically wear laboratory coats. The challenge of discovery comes with a competitive price. The foundation of the research laboratory is based upon the funding to continue its existence. According to the NIH FY 2009 budget proposal, the Special Statutory Funding Program for Type 1 Diabetes Research is $150 million. This is the same as it was in 2008. However the cost of research has not stayed the same. This is only one example of the research funding trends.

In order to become competitive and efficient, the business foundation must be re-established in the MMPCs. Continuing to meet the need for increased knowledge and new technology brings new research opportunities. With those opportunities comes an expansion in the market area of research. Consideration must be given to the mechanism and tools used to reach those areas. This concept of marketing and advertising has to be addressed. Increased consumer awareness has benefits on both sides of the spectrum. Several studies researched the price effect of advertising and its subsequent effect on consumer welfare. It is not surprising that these studies have extremely varying results, depending on the advertising viewpoint (persuasive, informative, and complementary). The welfare effect of advertising depends critically upon the influence of advertising on price and consumer preferences. Many studies have clearly shown that the price effect of advertising has important welfare implications when advertising attracts new customers, generates market externalities, or lowers consumer search costs (Shapiro, 1980). This helps to increase the attractiveness of the MMPCs.
The administrative challenges for funding can be met with strategic measures that level the playing ground. Leadership is only effective with planning and flexibility. The talent at the MMPCs are too numerous to mention. However, there is a need for administrative component with the power to implement and direct measures to ensure the viability of the MMPC and the consortium.

These recommendations are submitted with the upmost respect to the men and women who have dedicated themselves to improving the health of the nation and the world.

References
1. Department of Health and Human Services FY 2009 Budget referenced at: www.hrsa.gov/about/budgetjustification09
Appendix F

Johns Hopkins University Masters of Business Management Capstone Business Practices Survey

The JHU MBA Capstone team sent a survey to each MMPC and asked it to respond regarding its business practices. Responses are below in their entirety.

1. Case Western Reserve MMPC
2. University of Cincinnati MMPC
3. University of Texas Southwestern Medical Center MMPC
4. Washington University MMPC
5. Yale University MMPC
6. Vanderbilt University MMPC

1. Case Western Reserve MMPC

Operations
Work flow process:

With in each laboratory core how is work assigned?
When a test is ordered, the core that corresponds will meet with their personnel to do a plan of action and schedule the test/analysis.

How many tests can be done simultaneously?
Have not run into this circumstance as yet where work is scheduled simultaneously. It depends on the test. For example, in December 2008, we received multiple orders for “lipid synthesis”. We were able to batch together samples from various clients and get some work done in parallel. Likewise, we simultaneously received a request to measure body composition and a request to measure energy expenditure from two separate clients, since the assays are similar we were able to process in parallel.

What are the labor intensive outliers? Surgeries in the Metabolic Core, prepping of samples and analyzing data in the Analytical Core.

Does your site perform any special / unique testing?
The development of protocols for individual users/clients (especially small molecule tests). None of the tests/protocols are standard/routine. In the Analysis Core, the prepping of samples and the Analysis of data is usually a unique protocol depending on the client.

Do you have international request? What percentage of each? A few to date: an inquiry from Canada; however work has not been requested as yet. Also, one of our users/clients will be moving to Australia and will continue her request of services. . We have also consulted with a group from Japan regarding the use of various tracer methods, they are interested in establishing certain methods for measuring energy expenditure and protein synthesis and have exchanged emails, etc. to get things running.
Explain how ethics plays into your business model. Usual business practices; First come, First serve.

What is your ethics review process? The cores follow Case Western Reserve University, IACUC, IRB and OSHA guidelines. Reviews are given annually to maintain licenses.

How are collaborations documented and managed? This is one of the most difficult problems. The MMPC is the mechanism for the development of protocols, procedures. The expense/time/effort put into the development and validation pays nothing and results sometimes do not appear as an order for the MMPC. Much time and effort expended cannot be charged in real dollars to the MMPC.

Do you have performance improvement measures in place? Annual review processes; bi-weekly staff meetings; door open policy.

Supply Management:

How do you order your inventory? (In bulk or individually) Individually. What if any savings have been realized by this method? We rely on the relationships with vendors that deal with Case. We, the MMPC, do not order in bulk because this would be a waste of money. Most of our protocols are unique, and buying in bulk for them would not save us any money.

Does the University purchasing power help? The discounts realized are because Case Western Reserve University deals with many vendors daily. Also, we have a special relationship with the company that supplies us with stable isotopic compounds. We receive a discount on most catalogue items.

Staffing:

What is your staffing ratio? (Technical, Scientist, Administrative?) We have: 4 technicians; 6 scientists (3 are core-directors); 1 administrative manager.

What is your employee turn over rate? Very good, we have not needed to replace anyone for two years.

How do you get training to perform new or updated procedures? Vanderbilt Course in Clamps. Normal scientific updates (through reading or other scientists); P.I. makes modifications to protocols when needed.

How do you communicate internally and externally? By email, phone, and in person (both internally and externally). By phone, and email usual for external clients.

What is your work capacity? Our capacity cannot be easily quantified because of the large amount of time spent in educating users, developing protocols for them, and developing new assays. Actually, we are at the limit of our capacity with our current technical staff. Note that
since our MMPC is funded by a subcontract to the BCU (at about 60% of the budget of the full-fledged other MMPCs), we are severely strained in our work capacity. The education component is perhaps the most underappreciated aspect that affects time. For example, a typical scenario may involve consulting to establish the first experiment(s) that needs to be done, time to perform the analyses/review the data and time to discuss the meaning of the data and plan the next experiment(s). The last part is especially problematic since in some cases the outcome is not what was expected, consequently, the MMPC is in a position of coming to some common ground with the user(s) regarding the design of future studies. The Metabolic Core also teaches investigators the very basics of animal physiology and animal maintenance (tailing mice, breeding). Many of our investigators have never done animal experiments before; they have only done tissue culture experiments. There is much time and effort spent in educating investigators on how to plan animal experiments (fed vs. fasted states) and what parameters needed to be tested for their projects.

How do you safeguard your information/ study results? Keep in dedicated files, on Computers used for analysis; hard copies to clients. This Center offers individual study design which incorporates well on a database. Most of our clients are uninterested in having their information downloaded onto a national database.

Marketing

Who are your customers? We receive a few inquiries from Industry, however, almost all our clientele are repeat users from Academia. Our clients have diversified research interests, many outside the field of diabetes, which the Center was originally intended. Given that most of our clients interests are outside of diabetes, we cover a larger client base.

How do they contact your lab? By email, phone, and on-line order submission.

How does your center work with customer issues? We first consult as a group. Then the Core Director, where an order is referred, works with the client to develop a time frame, protocols, etc. Most clients do not realize the time involved from start to finish, nor what the test design entails. The co-director will usually have to modify a study design and tests before proceeding. In some cases, the client is turned away from a non-productive, useless experiment. In the long run this can only help our reputation.

How does your center promote client/ center collaboration? By keeping in touch with the clients on all aspects of their order. By giving them results that are based on actuality even if it didn’t turn out the way the client thought it would. By having an open door, call back protocol which develops into a user friendly Center. Our reputation is based on scientific approach/methods and quality of results.

Who are your repeats vs. new customers? Our repeat customers seem to be about 80% of our users. Most often clients within the University Community although we seem to be developing, by word of mouth, more outside cliental. The Analytical Core performs about 75% of its work for users outside of CWRU, in some cases this involves collaborating with
another MMPC (i.e. a biological experiment is performed by another MMPC and samples are analyzed at CWRU).

How do you find them? (How do they find you?) By word of mouth, advertising done via emails (mass emails to Cleveland Community), and billboards. Travel to meetings and speaking with other scientists sometimes develops into a Center/Client relationship. Mass e-mail from Dr Mare Laughlin to NIDDK grantees. We also are advertising on the plasma screen TVs within the School of Medicine at CWRU.

At what point is collaboration addressed? Collaboration on simple/standard services is not allowed. If a project involves developing complicated assays, we would consult with Dr Maren Laughlin to work out the terms of the collaboration, in accordance with rules spelled out in the RFA for MMPCs.

What is your marketing budget? n/a

What is your driving force for marketing? (Income, opportunity for unique samples/testing, etc.?) Provide techniques that very few laboratories have and some that are unique to this Center.

What is your competitive advantage? We are able to conduct experiments for our clients which they would be unable to do for themselves (would not have the resources to do themselves), i.e., animal surgeries, Mass Spectrometry on small molecule analysis, etc. We offer an array of tests that do not require transportation of mice to the MMPC. For example, clients can inject isotopes in their labs, collect and then ship samples. This minimizes costs to the client (e.g. shipping, quarantine, etc.) and increases the efficiency of throughput (e.g. MMPC staff concentrates on the analyses that we specialize in whereas the clients concentrate on managing the biological experiment).

How do you build customer loyalty/preference? By the quality of our work.

How do you get new customers? (Attractive pricing, Quality, Geographical preference?) We mention our Center at conferences, seminars that are attended by our Co-Directors. Word of mouth by our current/past clients.

What is the vision of the center? To educate and provide research tools to the large number of scientists who, over the past 25 years, have not learned about metabolism and metabolic techniques. The national course on “Training in tracer techniques” which we organize is also part of the vision. For the metabolic core we hope to increase the number of experiments and expand our services. In the next year we would like to be able to offer chronic and acute ICV infusions of leptin for obesity studies.

What is your strategic plan? The development of new techniques, and to further the education of our clients.
Do you have a business development plan? Follow new scientific advances and keep our science at the cutting edge.

Who else offers your service? Small fraction our assays/tests are offered at Yale. The Vanderbilt Center has parallel endeavors but not identical to us. Our efforts towards education have allowed other labs to establish some of our methods (e.g. groups in Texas, New York and Japan now regularly perform analyses of protein synthesis).

What is your reputation vs. Competitors? We have received no negative feedback from our clients. Our repeat users show what they think by continuing to use our Center.

Financial

How do you bill your clients? Internally, invoices emailed, an account supplies, internal journals done to directly bill their account. Externally, invoices are mailed.

What is your collection rate? Internally 100%; Externally, 100, even though the Administrative Manager may have to send out a second/duplicate invoice.

What is the average collection period from billing to receiving? Internally, same day. Externally; 30-60 days.

How much revenue do you take in? We have managed to increase our revenue by 140% since last year. The first year is not included since we were setting up and did not have a lot in place to handle any clients except for a few. In our Third year (@4/01/08) we received income of $32,974. Next year (our fourth year operating as a Center) we expect our annual income to be $60,000.

Final Question

What would you like to see improved about the current process? In spite of all the efforts from the MMPCs and Program Directors, many potential users (academic and industrial) are unaware of the opportunities available in the MMPC network.
2. University of Cincinnati MMPC

Operations

Work flow process:
The work flow process is similar in each core. Below is an example of the work flow process for our Animal Core.

Requests: Requests are received via email or applications are completed on the national MMPC website. Test description and price is emailed to the investigator along with an application for services. This application is filled out before performing the test to ensure that the correct information is obtained to perform the test and enter data in efficiently.

Samples:
After samples are received, they are given to the specific core technician that will be performing the assay. Expected completion dates are obtained and relayed to the investigator.

Animals:
Standard Operating Procedures for non-approved animal vendors are sent to the investigator. This explains Animal Health Reports and Quarantine options.
   Long-term: 8-week quarantine / animals can be returned
   Short-term: 10 day quarantine / terminal

Data Analysis:
Data are received from the core technicians after being checked by the core director, organized in a clear “user friendly” format, checked for errors, and sent to the investigator. Data is uploaded to the national database. Graphing and statistical analysis are performed as requested.

Invoicing:
After testing is complete, an invoice for services is sent to the investigator. Payment is collected and sent to accounts receivable to be deposited into the MMPC Revenue Account. All invoicing and payments received are tracked in a database created internally. Revenue account ledgers are checked and balanced.

Acknowledgement:
Inserts are placed inside all mailed invoices to remind investigators to acknowledge the center. PubMed searches are performed monthly.

Within each laboratory core how is work assigned? Technicians are assigned particular duties of the MMPC. The Animal Core has a technician assigned specifically for the receipt of animals, colony management, etc. The Lipid & Glucose Metabolism Core has particular technicians assigned for chemical assays, FPLC, clamping and others. The same is true of the Cardiovascular and Energy Balance Cores.

How many tests can be done simultaneously?
Multiple Core services can be performed with each Core technician simultaneously working on each request.

What are the labor intensive outliers?
These would include measurements that involve a massive amount of data generated (indirect calorimetry, telemetry, meal pattern measurements, echocardiogram, etc). This would involve quite a bit of tech. time for data analysis and presentation.

Does your site perform any special / unique testing?
A test most unique to our center is the lymph fistula mouse. Investigators request this service to measure chylomicron formation and secretion, and metabolism and lipid absorption. Another test frequently requested that is unique to our center is the non-invasive lipid absorption test. In addition, our site has starting liver perfusion studies for internal MMPC users with great success. Last, our telemetry studies have been increasingly popular.

Do you have international request? What percentage of each?
We have had several international requests. Though the number of international requests is few, many result in long-term studies or service contracts. One example is a new service
contract set up with Ajinomoto Inc, Japan to study the effect of amino acids on intestinal lipid absorption. In this study we will be measuring intestinal absorption and assimilation of lipids.

Explain how ethics plays into your business model.

In our business model the two ethical issues that we address are priority of testing and payment for service. There are no exceptions. Testing is on a first come, first serve basis. All investigators are expected to pay. However, if funding is limited to a young investigator, the center director will assist with payment through other sources of funding such as the Dean’s incentive fund.

What is your ethics review process?

This is reviewed annually by the internal advisory committee.

How are collaborations documented and managed?

All correspondence, meeting minutes, contracts are kept on file for each collaboration set up with the MMPC. Monthly meetings are arranged to discuss the study progress and next steps. Once the studies are completed, a presentation is kept on file as MMPC record.

Do you have performance improvement measures in place?

The UC MMPC asks three key questions when evaluating and implementing ideas for improvement.

- Are the cores contributing?
- Is there a plan for improving core output? Is there anyway to shorten the time taken to perform a particular test?
- Are members of the MMPC working together well?

Supply Management:

How do you order your inventory? (In bulk or individually)

One administrator orders for all MMPC cores. She will determine what is needed in bulk and individually. For instance, chemical assays are used daily for the MMPC. Once the supply is low these will be ordered in bulk. Items that aren’t needed in bulk, for example animal restraint tubes or calibration gases, would be ordered individually.

What if any savings have been realized by this method?

By having one administrator ordering supplies for all cores, saves on multiple orders and shipping fees.

Does the University purchasing power help?

Yes. It tends to lower overall cost.
Staffing:
What is your staffing ratio? (Technical, Scientist, Administrative?)

9 Scientist (includes directors) : 8 Technical : 1 Administrative

What is your employee turn over rate?

Attrition is incredibly low for the UC MMPC. All original directors and research technicians are in place. This allows for well trained and skilled technicians performing the studies of the phenotyping center. Student workers account for turn-over, but that is expected.

How do you get training to perform new or updated procedures?

Technicians are sent to training seminars through travel money provided by the Center Revenue Account and the Dean’s Incentive grant. Many times, a service representative will give training on site for any new equipment or procedures.

How do you communicate internally and externally?

Communication internally is primarily through email, phone calls, and monthly MMPC meeting. External communication is mostly by phone conversations, conference calls, and travel to the MMPC.

What is your work capacity?

This number is hard to define, for example, currently we are on average servicing 6-7 investigator requests per week.

How do you safeguard your information/ study results?

Investigator information and data is kept in a UC MMPC database that is backed up each evening. Only the director and administrator have access to this database.

Marketing
Who are your customers?

NIH funded investigators, investigators funded by other mechanisms, as well as outside companies.

How do they contact your lab?

We are contacted by email or phone.

How does your center work with customer issues?
As of yet, only a few very minor issues have come up. For instance, data cannot be delivered to the investigator as promised due to machine malfunction. We alert the investigator immediately of the problem.

How does your center promote client/center collaboration?

We promote collaboration by having direct communication with the investigator through phone conversations and emails in a timely fashion. The center director reminds the investigator that the MMPC is a service center.

Who are your repeats vs. new customers?

Around fifty percent of our requests come from repeat customers.

How do you find them? (How do they find you?)

Majority of the investigators that use the MMPC are referred by other users. The national MMPC website is also a good tool used for contact.

At what point is collaboration addressed?

Collaboration is only addressed if raised by the requesting investigator.

What is your marketing budget?

We do not have a marketing budget. Most of our business is generated through the national website and word-of-mouth.

What is your driving force for marketing? (Income, opportunity for unique samples/testing, etc.?)

n/a

What is your competitive advantage?

n/a

How do you build customer loyalty/preference?

We build customer loyalty/preference by the service we provide.

How do you get new customers? (Attractive pricing, Quality, Geographical preference?)

Word-of-mouth and unique tests offered by our center.
What is the vision of the center?

Our vision is to continue to provide quality service at a reasonable price and in a timely fashion to investigators.

What is your strategic plan?

Our strategic plan is to continue to establish new phenotypic tests for investigators and at the same time eliminate those tests that are not frequently requested by investigators. We believe such an approach makes the best use of our resources.

Do you have a business development plan?

n/a

Who else offers your service?

Some of our basic services are offered by other MMPC centers. This is inevitable due to the difficulty in shipping animals from center to center.

What is your reputation vs. Competitors?

n/a

Financial

How do you bill your clients?

Invoicing:
- After testing is complete, an invoice for services is sent to the investigator.
- Payment is collected and sent to accounts receivable to be deposited into the MMPC Revenue Account.
- All invoicing and payments received are tracked in a database created internally.
- Revenue account ledgers are checked and balanced.
- Revenue dollars are spent by different cores of the UC MMPC depending on special needs, service contracts, repair and replacement of existing equipment, and to support center investigators and technical staff to attend meetings and learn specific techniques in other institutions.

What is your collection rate?

We currently are at a 97.8% collection rate.

What is the average collection period from billing to receiving?

Sixty to ninety days.
How much revenue do you take in?

Our average revenue per year has been around $125,000.

Final Question
What would you like to see improved about the current process?

We believe our current process is working quite well. No current plans of change have been discussed.
4. UTSW MMPC

Work flow process:

With in each laboratory core how is work assigned? The UTSWMC MMPC operates essentially 2 cores, 1 that works on liver physiology and 1 that works on heart physiology. When a project is agreed upon, work is assigned in both cores in much the same way. Each core has a group of roughly 2 technicians that take on the biological aspect of the test (i.e. perfused organs or tracer infusions). Resulting samples (typically tissue, blood or metabolites from perfusate) are analyzed by NMR and the data is interpreted by the Core directors and communicated to the collaborator.

How many tests can be done simultaneously? Each core has the capacity to support about 3 projects in the pipeline at one time. Total throughput is approximately one project/core/month.

What are the labor intensive outliers? Perfusions, infusions, Sample processing. The real limitation to throughput is not labor, but access to specialized instrumentation (NMR spectrometers).

Does your site perform any special / unique testing? Yes. We focus solely on NMR isotopomer analysis of metabolic flux. This is a highly specialized approach to phenotyping that is not generally reproduced at the other sites.

Do you have international request? What percentage of each? Not often. Perhaps one international request is made per year.

Explain how ethics plays into your business model. The MMPC operates under the usual high standards of scientific and ethical rigor, but no special or specific ethical standards have been established for the MMPC process.

What is your ethics review process? No formal review process is in place. All university staff must participate in a basic ethics training course and pass a corresponding exam according to UTSWMC guidlines.

How are collaborations documented and managed? With very few exceptions, all projects taken on by the UTSWMC MMPC are collaborations. These collaborations are considered on a case by case basis. In general, only projects with hypotheses that are clearly addressable by NMR isotopomer analysis are accepted.

Do you have performance improvement measures in place? Performance is monitored throughout the testing process and changes are made ad hoc when necessary.

Supply Management:
How do you order your inventory? (In bulk or individually)? All supplies are ordered in bulk and used on each project as necessary.

What if any savings have been realized by this method? Unknown. Our most expensive supplies are stable isotopes, which can not be purchased individually.

Does the University purchasing power help? Yes. UTSWMC receive substantial discounts from most vendors.

Staffing:

What is your staffing ratio? (Technical, Scientist, Administrative?) Approximately 2:1:0 (Technician:Scientist:Administrative)

What is your employee turn over rate? Employee turnover is very low. Perhaps 1/year

How do you get training to perform new or updated procedures? This is rare, but usually via email/phone communications. Occasionally, travel to or from other sites.

How do you communicate internally and externally? Verbally or email. Small group meetings are organized within the cores.

What is your work capacity? 1 project/core/month

How do you safeguard your information/ study results? We use standard practices to protect notebook data and electronic data. All employees undergo information security training and must pass a corresponding exam administered by UTSWMC. Otherwise, no special practices are in place for the MMPC.

Marketing

Who are your customers? Other academic scientists who use mouse models to study obesity and diabetes

How do they contact your lab? By email or phone

How does your center work with customer issues? Throughput is low, so all issues are handled individually between staff and users.

How does your center promote client/ center collaboration? Our test are highly specialized and in many respects customized, so all interactions with users are considered collaborations (with some rare exceptions).

Who are your repeats vs. new customers? Most users end up as extended collaborations
How do you find them? (How do they find you?) Almost all of our interactions are initiated by word of mouth or by investigators who have read our publications.

At what point is collaboration addressed? This is addressed during the very first conversation. In fact, it has almost always been presumed by the investigator that the interaction would be in the form of a collaboration.

What is your marketing budget? $0

What is your driving force for marketing? (Income, opportunity for unique samples/testing, etc.?) We do not market per se, but we will sometimes contact a potential collaborator who has mice that have aspects that will obviously benefit by our unique tests.

What is your competitive advantage? Our test are unique, technically demanding and require specialized instruments and training to perform properly.

How do you build customer loyalty/preference? By providing important data that is not available or very difficult to obtain using other approaches.

How do you get new customers? (Attractive pricing, Quality, Geographical preference?) Users approach us, or on occasion we contact a potential user, with a mouse model amenable to the approaches we use.

What is the vision of the center? The vision of this center is to make metabolic flux measurements available to scientists with mouse models pertinent to the study of obesity and diabetes.

What is your strategic plan? To provide the greatest scientific impact possible by applying NMR based phenotyping methods to mice with genotypes significant to the etiology of disease. We can not provide these tools as a general method or in a screening capacity to all comers because we are limited by the low volume throughput inherent to these methods. An important part of our operating strategy is to identify the projects with the highest scientific impact and those with the greatest potential to benefit from the methods employed here.

Do you have a business development plan? Not really. We currently aim to recover approximately 50% of the costs of the experiments.

Who else offers your service? The services we offer are not duplicated by other MMPC sites. Case Western offers some closely related experiments.

What is your reputation vs. Competitors? We have no direct competition, but we seem to have a good reputation among scientists who have collaborated with us. I predict those who have collaborated with us might find the process a bit slow, but the nature of our methods dictates a slow pace. I find that most users are happy with the metabolic flux details that are measured here. Often the amount of information obtained from our tests is enough to support
the greatest part of a scientific publication.

Financial

How do you bill your clients? Investigators are sent an invoice

What is your collection rate? It is too soon to say; we’ve only been billing for about a year.

What is the average collection period from billing to receiving? 6 months

How much revenue do you take in? We bill approximately $3,000/ study

Final Question

What would you like to see improved about the current process? We are happy with the current process.
4. University of Washington MMPC

Operations
Work flow process:
With in each laboratory core how is work assigned?
Within each core there are specific research scientists and technicians that are responsible for the individual services that each core provides. So once an order comes in, whoever is responsible for performing the services requested will fit it into their schedule. For example, in our Diabetes core, Kayoko Ogimoto and Iaela David are the only ones who perform all body composition and calorimetry services, so once an order comes in it goes to them and they see how it will fit in to their schedule. The same goes for our Nephrology core. Kelly Hudkins, Mariko Koelling, and Tomasz Wietecha are in charge of services like processing, sectioning, and staining slides, while Jin Kim and Tom McDonald are in charge of specific services like Movats and atherosclerosis quantification. So whatever the order is for, is sent to the specific staff member who does that.

How many tests can be done simultaneously?
For the center as a whole, since our cores focus on different types of services, we can accommodate tests at each core simultaneously. However within the cores themselves it differs. For example, in our Diabetes core and Metabolic HUB we can only do tests on mice one order at a time because we don’t have enough equipment to accommodate more. If the orders contain say a low number of mice, then we could possibly test both orders at the same time, however that hasn’t happened yet. We have put in requests for supplemental funds in hopes to add more equipment and personnel funds in order to expand our capacity.

What are the labor intensive outliers?
Almost all of our tests are labor intensive. Morphometry, calorimetry, and cardiology testing all require highly skilled staff to perform them. We have an amazing staff with expertise in sectioning, surgery, and other skills required for the core tests. The only things that aren’t really labor intensive are tests from the Metabolic HUB (IPGTT, insulin tolerance) and the Analytical HUB (lipid analyses)

Does your site perform any special / unique testing?
As of now our unique tests are in development and we plan to offer retinopathy, vascular reactivity, and Doppler diastolic function heart testing, making us the only center to do these. However, although not unique, our services like morphology- especially atherosclerosis and kidney, energy balance by indirect calorimetry, and FPLC separation of plasma lipoproteins exceeds others. In addition, our Animal Core uses these Flex-Air units which no other center uses. These units house live mice when they come in and the advantage is that they can bypass quarantine and they can be moved from room to room when housed in these units.

Do you have international request? What percentage of each?
No international requests yet.

Explain how ethics plays into your business model.
There are several situations in which ethical considerations plays into our business model.
a) Investigators: a major goal is to treat each investigator equally in terms of their opportunities to utilize our MMPC. We do not pre-select users based on their location, institutional rank, gender, or type of institution.
b) Charge backs: we also try our best to make sure that charges are fairly determined based on the type and amount of work done. It would be quite easy to “pad” our invoice accounts, but we do not do this. It’s fair to say that we agonize over our invoicing quite often.
c) Study design: We do not want to partake in unnecessary work and do not want to charge investigators for studies which should not be done. Thus we work hard to advise investigators when they do not, and when they do, need specific procedures done. Such advice is based on what we understand of their projects following discussions with investigators.
d) Data: We report studies which work well and those that do not. We are honest and do not toss out data. We consider it to be of the utmost importance that investigators know exactly how each study was conducted and the outcomes. It is best if they can actually have the feeling of “having done the work themselves” and this has the best chance of occurring with complete transparency.

What is your ethics review process?
We do not have a formal ethics review process. Contact with investigators, study design, charges and data analyses/communication is done under an umbrella of mutual trust between the MMPC PI and Directors, and between MMPC and Investigators.

How are collaborations documented and managed?
Talks of collaboration begins between the MMPC directors and the investigators when initially going over their experimental design. This information is then passed on to the Center Administrator that way correct pricing is used as well as all documentation of publications resulting from this collaboration is received. In addition to this, we send out an annual email requesting all investigators who used our center to send information on any publication in which the MMPC is acknowledged and we ask that they do acknowledge our center in all publications using the data they received from us.

Do you have performance improvement measures in place?
We were able to improve on one facet, our database. That was an area we definitely needed to improve on, so with the proper training we were able to assign someone to be in charge of data entry. For now we do not have any measures in place, but we are constantly trying to make the administrative process run smoother. There are small issues that arise when say investigators send samples or requests tests directly from the core without properly applying for services online first. This doesn’t create a huge mess or anything, but if there was a standardized process that everyone followed I know administratively, it would run more smoothly.

Supply Management:
How do you order your inventory? (In bulk or individually)
Depending on the item we order both in bulk and individually. General supplies like tubes, slides, etc. are ordered in bulk as they are used constantly. Other supplies which are specific to individual tests are ordered individually. For example in our Analytical HUB all kits are only ordered when a request for that service is placed.
What if any savings have been realized by this method?
Buying in bulk will always save money on supplies that are used at a constant rate, so we do save by doing this for general supplies. For things like the analytical kits that we order separately it may be more expensive than ordering in bulk, however if we were not to use that kit, we would be losing more money than the money saved by ordering in bulk.

Does the University purchasing power help?
Yes. It keeps the scientists and technicians focusing on working on the tests as with minimal administrative duties.

Staffing:
What is your staffing ratio? (Technical, Scientist, Administrative?)
Administrative – 3 (Center Director, Center Co-Director, and Center Administrator)
Scientist – 18 (9 Core Directors & Co-Core Directors and 9 Research Scientists)
Technical – 5 (1 Research Technologist Supervisor, 2 Research Technologists, 1 Histologic Technician, and 1 Student Assistant)

What is your employee turn over rate?
We’ve only lost 2 employees and a 3rd one that went into retirement in the 3 years we’ve been running.

How do you get training to perform new or updated procedures?
If there is training needed for specific core services, the cores coordinate training amongst themselves. For center wide trainings, the center administrator coordinates this. For example the new MMPC database training was scheduled by the center administrator and had the proper folks fly out and train.

How do you communicate internally and externally?
For the most part it is done via email. The cores are located on different parts of campus and with everyone’s busy schedule email is the best way, however phone conversations definitely take place when needed. Communicating with the investigators is also done largely via email. We also have a monthly director’s meeting for the Seattle Core Directors, and a monthly teleconference amongst all the MMPCs, and an annual meeting for all the MMPCs to physically meet up.

What is your work capacity?
This is different for each core and each test. A few examples are as follows:
Diabetes and Energy Balance Core
• Body composition – usually about 30 mice/day, but are able to do up to 50/day
• Calorimetry – 8 mice every 36 hours
Metabolic HUB
• IPGTT – 12 mice/day
• Insulin Sensitivity – 12 mice/day
Analytical HUB
• Lipid extraction – 2 orders/week with less than 20 samples/order
• FPLC – 3 samples/day
• TC/TG – 200 samples/day
• Adipokines – 76 samples over 2 days

How do you safeguard your information/ study results?
Data is obtained by the MMPC research staff and is later examined by the MMPC core directors. These data are then given to Rick McIndoe. We also retain data copies and generate final reports containing methodology, raw, and analyzed data.

Marketing
Who are your customers?
Our customers are investigators from other universities, research institutes, and industry

How do they contact your lab?
It usually just starts out with an email to the center administrator and from there the inquiry is directed to the appropriate core to discuss experimental design. When the order is ready to be placed they are directed back to the administrator to complete the process.

How does your center work with customer issues?
They usually go through the center administrator usually and then if applicable, are directed to the core laboratories for their input. However if it’s purely scientific, the investigators just go directly to the lab staff for their inquiries.

How does your center promote client/center collaboration?

Who are your repeats vs. new customers?
For the most part almost half our customers have repeated business with us. This goes for internal UW orders, other universities and research institutions, and industry. A few examples are – Warren Ladiges and Michael Chin from UW, Moshe Levi from University of Colorado, Eva Feldman from University of Michigan, Katherine Tuttle from Providence Medical Research Institute, Thomas Wight from Benaroya Research Institute, and Sandra Schreyer from Boehringer Ingelheim.

How do you find them? (How do they find you?)
Connections from our core directors help as well as simple word of mouth from other investigators who have had previous work with us. At times when core directors are aware of a project that can benefit from our services they will approach those investigators and let them know what we offer.

At what point is collaboration addressed?
From the very beginning, it is established whether or not this order will be a collaboration or not.

What is your marketing budget?
We don’t really have a specific marketing budget. So far our only “official” marketing has been hanging posters and brochures on campus. In addition we give brochures for those travelling to science meetings where there could be possible clients. Word of mouth and networking from the core directors has been our main source of business.
What is your driving force for marketing? (Income, opportunity for unique samples/testing, etc.?)
Definitely income and recognition in investigators’ publications and grants. In addition to monetary units, acknowledgement statements from investigators who are published or who have grants that are funded is one index of success the NIH uses for the MMPCs.

What is your competitive advantage?
Out of the 6 MMPCs we are 1 of the 3 “full” centers. While other centers sort of specialize in certain fields, Vanderbilt, Cincinnati, and Seattle are the only 3 that are “full service” centers. We have 3 cores, plus 2 additional hubs, and we are in the process of introducing another hub. This new hub will be the only one out of all the MMPCs that will study vascular reactivity connecting studies in urology and diabetes. This is a new direction for the consortium as a whole. In addition we are the only center on the west coast. The closest MMPC to us is the one in UT Southwestern, but again they are not a full service center.

How do you build customer loyalty/preference?
Actually our work pretty much speaks for itself. Investigators are truly pleased with their data and the methods that we use. We also try to make the process as seamless as possible by coordinating shipping, transport, and paperwork over here and only requesting necessary information from investigators when necessary.

How do you get new customers? (Attractive pricing, Quality, Geographical preference?)
As mentioned before, we get customers because we are the only full service center on the west coast. Our pricing is comparable to other centers, and the quality of our work is excellent.

What is the vision of the center?
The vision is to have a vibrant, active center which is known for excellence of our data and consultation services. We would like to maintain the current activity level in the Micro/Macrovascular core, increase usage in the Cardio core and in the energy balance arm of the Diabetes core. We would like to ensure that the cored directors and their staff are able to maintain their own research projects while conducting MMPC activities. It is of critical importance that the science productivity for the core directors is not threatened by excess or “overwork” status driven by the MMPC.

What is your strategic plan? Do you have a business development plan?
For the most part we do not have one. This is a weakness that we would like help with. One exception is to provide rate glucose clamping as a way to obtain program income, which can then be used to “grow” the mouse clamping or energy balance components of the Diabetes Core. Another example is the Micro/Macrovascular core which has been able to obtain program income in sufficient amounts to be able to pay increase fte salary. Thus we generally get the concept of using program income to “grow” the MMPC, but don’t have a formal business plans to do this. We are in the “seat of the pants” right now.

Who else offers your service?
Vanderbilt and Cincinnati are the 2 other centers that offer the similar range in services to our center, but we have similar tests w/all other centers.

What is your reputation vs. Competitors?
I think our reputation is great considering that we are the newest MMPC compared to the others. Although our “competitors” have been around longer, thus will maintain their client list, we are constantly growing every year, doubling the number of investigators we perform work for and almost quadrupling the number of samples/animals we receive.

Financial
How do you bill your clients?
Once the work is completed, the lab staff send the center administrator the final estimate worksheet and then I bill on a monthly basis.

What is your collection rate?
I would say 100%. If there is an instance where there is a delay, it’s usually just an administrative oversight or some small billing complication. We always get paid for our services without any contenttion.

What is the average collection period from billing to receiving?
For the most part is it about a month or two. Some orders have delays for a small reason or another, but they usually come within a month. We receive payment for internal orders within a couple weeks after the monthly billing is sent out as all they have to do is put the charge on the internal budget the investigator provides when placing the order.

How much revenue do you take in?
The first year was $8,338 year 2 was around $93,046, and year 3 is at $103,297 with 4 more billing months left in our fiscal year.

Final Question
What would you like to see improved about the current process?
As mentioned before, a business plan as a whole is needed. While we are doing great in our current process, it would be nice to see goal plan to truly index our success. Scientifically we’d like to increase our “special/unique” testing and outside live animal orders. While we have the Flex-Air units that are a definite advantage for live animal orders, we haven’t seen a great demand for them yet.
5. Yale University MMPC

**Operations**

**Work flow process:**

**With in each laboratory core how is work assigned?**

**In-Vivo Physiology Core:**
- Technician: some husbandry duties, body composition studies and metabolic cage studies, assist with clamps
- Surgeon: Surgery (3 days/week)
- Post-docs: Executing in vivo studies (clamps, gtt’s), data analysis, tissue and plasma processing
- Faculty: Planning studies and communicating with other investigators, data analysis, reviewing manuscripts

**Metabolomics Core:**
- Receive request for services through website.
- Requests are prioritized with respect to time received and critical needs (i.e. grant submission deadlines, manuscript resubmissions are given more weight)
- Analyses are batched to maximize efficiency of instrument usage.
- Technicians: process samples, instrumental analysis, data processing.
- Faculty: Planning studies and communicating with other investigators, data analysis, reviewing manuscripts

**How many tests can be done simultaneously?**

**In-Vivo Physiology Core:**
- Within the in vivo core, it takes about 2-3 weeks to finish a set of studies on a particular mouse. At the same time, other mice are being worked through the phenotyping process. At any one time, 2-3 groups of mice may be in the phenotyping process

**Metabolomics Core:**
- Samples are analyzed on multiple instruments running at all times. On a typical day, ~ 4 to 6 tests are being run simultaneously.

**What are the labor intensive outliers?**

**In-Vivo Physiology Core:** The hyperinsulinemic-euglycemic clamp

**Metabolomics Core:**
- Sample preparation, setting up, running and monitoring instruments, data processing, data entry into the website.

**Does your site perform any special / unique testing?**

**In-Vivo Physiology Core:** The hyperinsulinemic-euglycemic clamp, metabolic cage studies, body composition

**Metabolomics Core:** Fatty acid metabolite profiles by lc/ms/ms.

**Do you have international request? What percentage of each?**

**In-Vivo Physiology Core:** Yes. 90-95% domestic, 5-10% international.

**Metabolomics Core:** Yes. ~2-5% international.

**Explain how ethics plays into your business model.**
We report the data as we generate it, even if it is contrary or problematic for the investigators hypothesis. We take the time to explain the data to our collaborators to prevent over interpretation or mis-interpretation.

**What is your ethics review process?**
Not formally, but the peer-review publication process serves as a checks and balances process.

**How are collaborations documented and managed?**
We usually have an MTA in place. Data is sent to collaborators when studies are complete. Collaborators will send us manuscripts for review prior to publication.

**Do you have performance improvement measures in place?**
We do check the quality of every metabolic cage and clamp studies and are vigilant for any problems that arise.
Metabolomics Core: Yes. Quality control samples are run with each batch of samples.

**Supply Management:**
How do you order your inventory? (In bulk or individually)
Usually in bulk, if possible.

What if any savings have been realized by this method?
Estimate, we save ~20% by purchasing in bulk.

**Does the University purchasing power help?**
Yes

**Staffing:**
What is your staffing ratio? (Technical, Scientist, Administrative?)
In-Vivo Physiology Core: 1 Faculty, 4 post docs, 1 full time technician, 1 part time (60%-surgeron) technician
Metabolomics Core: 1 Faculty, 2 full time technician, 1 part time (10%) administrative help.

What is your employee turn over rate?
In-Vivo Physiology Core: Postdocs / technician about every 2-3 years.
Metabolomics Core: 1 technician every 2 to 3 years.

How do you get training to perform new or updated procedures?
N/A
Metabolomics Core: Director –led training sessions.

How do you communicate internally and externally?
Weekly internal meetings. External communication mostly via e-mail or teleconference.

What is your work capacity?
~450 clamp studies/year
Metabolomics Core: ~17,000 assays per year

How do you safeguard your information/ study results?
All data is stored electronically with redundant copies. Hard copies are kept within the laboratory.
Marketing
Who are your customers?
~90% Academic, 10% industry
How do they contact your lab?
In-Vivo Physiology Core: 95% via personal contact (either Dr. Shulman or Dr. Samuel), 5%,
Website
Metabolomics Core: 25% via personal contact (either Dr. Shulman or Dr. Cline), 75%,
Website

How does your center work with customer issues?
Each study is customized for the client

How does your center promote client/center collaboration?
In-Vivo Physiology Core: We offer all new clients the chance for fee-for-service or collaboration. Almost all academic clients chose collaboration. We maintain the collaboration with frequent and clear communication with the client.
Metabolomics Core: We offer all new clients the chance for fee-for-service or collaboration, but encourage fee-for-service. Most choose fee-for-service.

Who are your repeats vs. new customers?
In-Vivo Physiology and Metabolomics Core: Repeat customers are usually academic investigators

How do you find them? (How do they find you?)
In-Vivo Physiology Core: Meet potential clients at meetings, invited talks or from past collaborations on non-MMPC projects.

At what point is collaboration addressed?
In-Vivo Physiology Core: In the planning stages of the experiments, prior to any shipment of animals.

What is your marketing budget?
$0.00

What is your driving force for marketing? (Income, opportunity for unique samples/testing, etc.?)
What is your competitive advantage?
We offer exceptionally high quality data which helps papers get published. We share our unique insights into the physiology of a particular mouse, insights that have been tempered by many years of studying myriad rodent models of obesity and insulin resistance.

How do you build customer loyalty/preference?
We provide customers with high quality data.

How do you get new customers? (Attractive pricing, Quality, Geographical preference?)
Word of mouth from past collaborators. Reputation of PI (Shulman)

What is the vision of the center?
To continue to lead the field and provide clients with exceptional data and insights into their particular mouse models. We would like to continue to expand our palette of phenotyping tests to include ß-cell physiology and in-vivo MRS studies.
What is your strategic plan?
We would like to cultivate a greater percent of industry clients. Support garnered from these studies will then be used to subsidize academic studies.

Do you have a business development plan?
No.

Who else offers your service?
Vanderbilt currently. Case Western and Cincinnati may start doing clamp studies in the near future. Several academic labs also can perform clamps. Vanderbilt, Case Western, and Cincinnati all offer many of the analytical services.

What is your reputation vs. Competitors?
Outstanding.

Financial
How do you bill your clients?
We prepare an invoice that is routed through our Endocrinology Business Manager.

What is your collection rate?
We anticipate it will be near 100% as all clients agree to pay for services before sending mice.

What is the average collection period from billing to receiving?
~3 to 6 months.

How much revenue do you take in?
Metabolomics Core: ~$30,000 to $40,000 per year.

Final Question
What would you like to see improved about the current process?
1) Centralized billing supports to track down relevant charges and handle transfer of monies.
2) More central administrative support for data upload and database management.
1. Vanderbilt University MMPC

Operations

Work flow process:
With in each laboratory core how is work assigned?
Work is assigned according to the requested procedure and entails many variables, such as the particular expertise of the research staff; number of studies to be done, whether mice will be shipped from a vendor or will enter Vanderbilt's 6-7 week quarantine and the anticipated length of time each procedure will take to completion.

How many tests can be done simultaneously?
Varies depending on what type and number of tests are requested. For example, clamping mice in the Metabolic Pathophysiology Core, Carlo can perform surgery (catheterizations) on 4 mice per day After the mouse recovers from surgery, Tasneem and Emily can then perform 4 clamp studies per day After the clamp studies are done, the analysis of the data is generated and summarized and a report is given to the investigator. Based on prior experience, the Core Directors have developed a good estimate for the time needed to perform tests.

What are the labor intensive outliers?
MPC: Surgeries, clamps, animal husbandry, tissue analysis Cardiovascular. Echo acelimitation ARC: FA TLC.

Does your site perform any special/unique testing?
- Cardiovascular Core Renal function, blood pressure, and measurement of circulating cardiovascular risk factors.
- Education Program
- Tissue imaging and pancreatic islet isolation subcores of the Metabolic Patho Core

Do you have international request? What percentage of each?
Yes. Education - 5%; Services - 2 %.

Explain how ethics plays into your business model.
It does not.

What is your ethics review process?
Review by Steering committee

How are collaborations documented and managed?
The MMPC does not collaborate. If a Vanderbilt investigator wishes to collaborate, then he is billed and pays the MMPC for the services.

Do you have performance improvement measures in place?
Yes. Vanderbilt University has a comprehensive "goal based" performance evaluation system which is done on a yearly basis. This evaluation pertains to and is used for MMPC
employees. Also, Vanderbilt has an "Elevate" program whereby employees are recognized and rewarded for outstanding performance.

**Supply Management:**
How do you order your inventory? (In bulk or individually)
*Supplies are ordered in bulk when possible.*

What if any savings have been realized by this method?
*Substantial savings have been realized by ordering in this manner. For example, ordering diabetes test strips from American Diabetes Wholesale offers a 50% savings.*

Does the University purchasing power help?
*Vanderbilt Purchasing has negotiated discount pricing for preferred vendors. We order from these vendors whenever practical.*

**Staffing:**
What is your staffing ratio? (Technical, Scientist, Administrative?)
*Technical - 17
Scientist - 15 (core directors and liaisons)
Administrative - 2 (Fran and Gary Bock in Finance Office) Some core managers, such as Wanda Sneed in the Hormone Core, assume administrative duties for their core.*

What is your employee turnover rate?
*Estimated at less than 1%. Over the last 4 years, we lost 2 people to industry, 1 to another university and the death of 1 colleague to cancer.*

How do you get training to perform new or updated procedures?
*If new equipment is purchased, training is done by the manufacturer. Core Directors and Managers train new employees. Procedures are constantly tweaked and evaluated and improved if needed.*

How do you communicate internally and externally?
*Communication is done at weekly lab meetings, seminars and e-mails. External communication is done by teleconferencing, e-mails, phone calls and meetings.*

What is your work capacity?
*Core dependent and test specific*

How do you safeguard your information/study results?
*The MMPC website is a secure password protected portal for sharing data and information with investigators. Vanderbilt also offers a server which is backed up nightly and external back-up drives are utilized on various computers.*

**Marketing**
Who are your customers?
*Our customers are investigators from inside Vanderbilt as well as investigators from other
universities and companies who are interested in diabetes and diabetes-related research.

How do they contact your lab?
*Vanderbilt investigators can contact us directly or if outside Vanderbilt, through the MMPC website.*

How does your center work with customer issues?
*Core directors, managers and research assistants work closely with customers and address any issues they may have.*

How does your center promote client-center collaboration?
*The MMPC centers all work closely together and referrals are made to other centers if the client's need's can best be met at another center. In some cases, more than one center will perform tests for a client. Also, all tests are listed by center in the catalog on the MMPC website and the client can select which center to place an application with.*

Who are your repeats VS. new customers?
*Many repeat customers.*

- **MPC** - 138 users, 26 Education, 13 no repeat
- **Cardio Core** - 69 users, 18 no repeat
- **Lipid Core** - 48 users, 15 no repeat

How do you find them? (How do they find you?)
*They find us from NIH generated promotions, word of mouth, publications*

At what point is collaboration addressed?
*Outset*

What is your marketing budget?
*0*

What is your driving force for marketing? (Income, opportunity for unique samples/testing, etc.?)
*Our responsibility to the scientific community and NIH. Acting in a manner consistent with the RFA*

What is your competitive advantage?
*Expertise*

How do you build customer loyalty/preference?
*Good data I hope*

How do you get new customers? (Attractive pricing, Quality, Geographical preference?)
*Quality, -*

What is the vision of the center?
To have a center that establishes methods, guidelines, and standards for the field. Be responsive to the scientific community.

What is your strategic plan? 
*Publish guidelines and standards. Conduct the center education*

Do you have a business development plan? 
*Not really. Adapt needs to run a revenue neutral business*

Who else offers your service? 
*MPC: Everyone but UTSW*  
*CPC: UW* 
*ARC: Yale, UW, Cincinnati*

What is your reputation vs. Competitors? 
*We are highly skilled, but considerably more expensive*

**Financial**

How do you bill your clients? 
*Fees for services are calculated based on the following formula:*

\[
\text{Technician Time} \times \text{Technician Salary Rate} (\$) \times ? \times \text{Recovery Factor} + \text{Cost of Materials} \times \text{Success Rate} \text{ (See example attached)}
\]

*Clients are invoiced once the service is completed using Quickbooks.*

What is your collection rate? 90-95%

What is the average collection period from billing to receiving? 30 - 60 days

How much revenue do you take in? $300,000-$400,000.

**Final Question**

What would you like to see improved about the current process? 
*Decrease overlap in services. I would like to see different centers use common business practices.*
Appendix G

A. Isotope Tracers in Metabolic Research

Student Evaluations

Summary: Oct 8-12, 2007

1. Were your expectations met?

<table>
<thead>
<tr>
<th>Experience</th>
<th>Human subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (not at all)</td>
<td>1 (not at all)</td>
</tr>
<tr>
<td>2 (limited)</td>
<td>2 (limited)</td>
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<td>3 (some)</td>
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</tr>
<tr>
<td>4 (substantially)</td>
<td>4 (substantially)</td>
</tr>
<tr>
<td>5 (fully)</td>
<td>5 (fully)</td>
</tr>
</tbody>
</table>

2. Were course faculty available and approachable?

<table>
<thead>
<tr>
<th>Experience</th>
<th>Human subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (not at all)</td>
<td>1 (not at all)</td>
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<tr>
<td>2 (limited)</td>
<td>2 (limited)</td>
</tr>
<tr>
<td>3 (some)</td>
<td>3 (some)</td>
</tr>
<tr>
<td>4 (substantially)</td>
<td>4 (substantially)</td>
</tr>
<tr>
<td>5 (fully)</td>
<td>5 (fully)</td>
</tr>
</tbody>
</table>

3. If you talked to faculty privately, or asked questions after lectures, were discussions or answers helpful?

<table>
<thead>
<tr>
<th>Experience</th>
<th>Human subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (not at all)</td>
<td>1 (not at all)</td>
</tr>
<tr>
<td>2 (limited)</td>
<td>2 (limited)</td>
</tr>
<tr>
<td>3 (some)</td>
<td>3 (some)</td>
</tr>
<tr>
<td>4 (very)</td>
<td>4 (very)</td>
</tr>
<tr>
<td>5 (fully)</td>
<td>5 (fully)</td>
</tr>
</tbody>
</table>

4. How would you rate the quality and usefulness of the lectures?

<table>
<thead>
<tr>
<th>Experience</th>
<th>Human subjects</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2 (good)</td>
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<tr>
<td>3 (very good)</td>
<td>3 (very good)</td>
</tr>
<tr>
<td>4 (excellent)</td>
<td>4 (excellent)</td>
</tr>
<tr>
<td>5 (outstanding)</td>
<td>5 (outstanding)</td>
</tr>
</tbody>
</table>
5. Were the lectures, on average, easy to understand?

<table>
<thead>
<tr>
<th>All respondents</th>
<th>Experience = 1-2</th>
<th>Experience = 3-4</th>
<th>Human subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (too easy)-0</td>
<td>1 (too easy)-0</td>
<td>1 (too easy)-0</td>
<td>1 (too easy)-0</td>
</tr>
<tr>
<td>2 (slightly simple)-2</td>
<td>2 (slightly simple)-2</td>
<td>2 (slightly simple)-0</td>
<td>2 (slightly simple)-0</td>
</tr>
<tr>
<td>3 (just right)-9</td>
<td>3 (just right)-5</td>
<td>3 (just right)-4</td>
<td>3 (just right)-8</td>
</tr>
<tr>
<td>4 (slightly hard)-19</td>
<td>4 (slightly hard)-11</td>
<td>4 (slightly hard)-8</td>
<td>4 (slightly hard)-13</td>
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<tr>
<td>5 (too hard)-2</td>
<td>5 (too hard)-1</td>
<td>5 (too hard)-1</td>
<td>5 (too hard)-2</td>
</tr>
</tbody>
</table>

Are there specific topics that you would like to see explained in an easier way, or with more detail/complexity?

Want more problems, and problems for all lectures
Want more time spent on equations
Want more NMR analysis
More details on the basics and the methods
Lectures were too rushed, too many lectures
More optional lectures would be better, with smaller groups
It was a good mix between difficult and easy lectures
Needed more on steady state and non-steady state techniques

6. Was the homework helpful and appropriate, and did morning problem sessions serve to answer your questions?

<table>
<thead>
<tr>
<th>All respondents</th>
<th>Experience = 1-2</th>
<th>Experience = 3-4</th>
<th>Human subjects</th>
</tr>
</thead>
<tbody>
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<td>1 (no)-0</td>
<td>1 (no)-0</td>
<td>1 (no)-0</td>
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<td>2 (limited)-3</td>
<td>2 (limited)-0</td>
<td>2 (limited)-3</td>
</tr>
<tr>
<td>3 (somewhat)-18</td>
<td>3 (somewhat)-10</td>
<td>3 (somewhat)-8</td>
<td>3 (somewhat)-8</td>
</tr>
<tr>
<td>4 (very)-9</td>
<td>4 (very)-5</td>
<td>4 (very)-4</td>
<td>4 (very)-4</td>
</tr>
<tr>
<td>5 (fully)-2</td>
<td>5 (fully)-1</td>
<td>5 (fully)-1</td>
<td>5 (fully)-8</td>
</tr>
</tbody>
</table>

7. Would you consider returning for this course in the future, or recommending it to students or colleagues?

<table>
<thead>
<tr>
<th>All respondents</th>
<th>Experience = 1-2</th>
<th>Experience = 3-4</th>
<th>Human subjects</th>
</tr>
</thead>
<tbody>
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<td>1 (no)-0</td>
<td>1 (no)-0</td>
<td>1 (no)-0</td>
<td>1 (no)-0</td>
</tr>
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<td>2 (maybe)-2</td>
<td>2 (maybe)-2</td>
<td>2 (maybe)-3</td>
</tr>
<tr>
<td>3 (depends on topics)-12</td>
<td>3 (depends/topics)-7</td>
<td>3 (depends/topics)-5</td>
<td>3 (depends)-8</td>
</tr>
<tr>
<td>4 (very likely)-6</td>
<td>4 (very likely)-2</td>
<td>4 (very likely)-4</td>
<td>4 (very likely)-4</td>
</tr>
<tr>
<td>5 (absolutely)-10</td>
<td>5 (absolutely)-8</td>
<td>5 (absolutely)-2</td>
<td>5 (absolutely)-8</td>
</tr>
</tbody>
</table>
1. Please rank your level of experience with tracers on a 5-point scale.

1 (none) 25.81% (8)
2 (limited) 45.16% (14)
3 (some) 22.58% (7)
4 (substantial) 6.45% (2)
5 (expert) 0% (0)
Total 31

2. What systems do you work in?

Cell Culture 32% (13)
Mice 40% (16)
Rats 22% (9)
Large Animals 17% (7)
Humans 28% (11)
Total Respondents 31
skipped question 9

3. What did you hope to learn at the Isotopic Tracers Course? (Check all that apply)

Basic tracer theory 27
Radioactive isotopes in whole body studies 14
Stable isotopes—whole body/isotopic dilution 23
Stable isotopes—mass spec techniques 23
Stable isotopes— isotopomer analysis 21
Stable isotopes—NMR isotopomer techniques 12
Stable isotopes—NMR whole body techniques 10
Nutrient metabolism techniques (carbohydrate, protein, lipid) 25
Models for tracer studies 16
Total Respondents 30
skipped question 10

Other?
1. radioactive/stable isotopes in cell biology and other organism studies (tissue culture cells or other model i.e. worm and fly). I will be appreciate if I can get some classic reference in those areas.
2. The variety of topics offered was excellent. I found it very useful to learn of alternative approaches with an emphasis on their strengths and limitations. It provided a very good roadmap for thinking of ways to utilize this methodology in my future research. It also provided an excellent network of potential contacts for advice as I proceed.

3. Logistics, costs and considerations for implementing and performing tracer studies in humans.

4. clarification of current understanding of principles and assumptions. Develop understanding of broader uses of isotope tracers than current experience.

5. Were your expectations met?

Not At All 0
Limited 5
Some 10
Substantially 15
Fully 3
Total Respondents 32
(skipped this question) 8

Comments?

1. Based on the info provided in the syllabus I was under the impression that more time would be allotted to discussing specific issues/methods in lipid synthesis than was actually given in lecture time. Fatty acid synthesis was only very briefly gone over, particularly with regards to deuterium use for such measurements. In addition, cholesterol synthesis was not even covered at all, save for a 1/2 slide mention that was only addressed very minimally in the question period. There was a definite lack of info available on lipid-centered techniques, whereas glucose and protein both got individual blocks of time.

2. For new learner, need much introduction.

3. Excellent course

4. Some parts are too hard for me to understand, because I didn't do these experiments. If add more information about application, it will be better.

5. Knowledgeable presenters who were generous with their time the entire week.

6. The course provided the fundamentals of isotope tracer approach. I found it very helpful in modifying certain aspects of my research. It also provided me with an opportunity to evaluate the techniques I am using and add new metabolic branches to my research.

7. My research focus involves the cellular metabolism stable isotopes (mostly 13C). The whole body methodology is less applicable to my research, but was very interesting.

8. I would suggest to break course into two separate sections: novice and intermediate. The course could be alternated year to year. This way, topics for true beginners and those already doing could be tailored more effectively. A progression could be for the novice to return the next year after some experience.

9. I was expecting less discussion of results and more details on analytical theory and techniques.

10. This course does a great job of addressing the multiple questions of a broad interest range.
11. More practical applications and hw problems (potentially in groups) would help to translate the theory to practice. In addition, methods and descriptions of procedures to prepare isotopes/primes/albumin binding/derivitization/instrument parameters would also help transfer theory into practice.
12. Most materials were just too hard for me.
13. Some lectures were too much detailed with real data. I expect more overview of general issues.
14. A lot of redundant information in the presentations. Could condense down to 3 days. The conference is very long, making it hard to stay focused and continue to absorb the needed information during the end of the week.
15. It will be much better to have defined questions and give more detailed experimental designs, instead of just the concepts and problems associated with the techniques. By the end of the course, I would like to know exactly how to do the experiments. If time limit is a factor, wouldn't it be nice to divide the students into interest groups?
16. This was a great course. I would recommend it to anyone interested in using isotopic tracers in their research, or even if they are currently using tracers.
17. Course was very informative.
18. I had ever had such in-depth training on the whole spectrum of tracer techniques. I found the broad coverage helpful since it allows me to assess the strengths and weaknesses of my techniques in comparison to others. I also found the in-depth discussion of mass-spec considerations helpful since I have always done the modeling and the animal/subject work, but not the mass spec work itself.
19. I would like to know more about the basics of how to use tracers in terms of Methods. How much tracer is necessary for cell culture, mouse, or other animal.
20. This was a very informative, comprehensive course. As a novice to the field, I highly recommend the text book in tandem with the lectures. I also appreciated the blend of students, post-docs, academic faculty, NIH scientists, and other scientists together in one setting.
21. I think it would be better to move the student presentation session to an earlier day. This session is really helpful.
22. I also want to learn some real experiment design. The course covers most of the theoretical basis, but gives little on how to design a real experiment.

6. What topics would you like to see covered in future meetings, or what presented topics are of no interest? What was the best thing you learned?

1. I would've liked to see a full section on lipid metabolism that includes fatty acid oxidation (which was discussed) but also synthesis as well, and a section on cholesterol or other sterol synthesis using particularly deuterated water, since it seemed from general consensus that the D2O method is far preferred for lipid synthesis over labeled acetate methods. Perhaps also have concurrent streams for those who are interested in radioisotopes and separate for stable isotopes, as there are those of us who have never worked with radioisotopes and likely have no intention to (particularly for those of us who work with humans as we would never give radioisotopes to those subjects). Also just as an aside, please ask presenters to use a light or white background for slide presentations, as darker backgrounds make it difficult to make notes on the slides, and use up lots of ink if printed.
2. double label water and energy expenditure measurement is the best thing I learned.

3. I would be nice to get some more examples and discussion for use of those techniques in cells.

4. It is good to learn all isotope techques to study mechanism in one week.

5. The best things I learned is the difference in glucose metabolism between mouse and human.

6. stable isotopic techniques

7. Even though the course provided a comprehensive overview of the basics, I would like to see more variations and applications of the approaches.

8. Please see my answer in 7

9. I would like to learn more about software and other research tools to enable isotope-based research.

10. I would like to see more specific information on the isotope techniques including practical techniques on handling, use and specifically analysis--starting from what information to get off of the GC/MS and then how to draw conclusions from this information.

11. I feel that going forward the things that I learned that will be most beneficial are the basic assumptions and calculations, as well as the pitfalls of these methods.

12. The most important take home was a structured and explicit list of issues that need to be considered that are typically left implicit in the literature. This will be most useful in designing my own experiments

13. Costs, considerations and implementation of tracer studies. Potentially have groups design a problem/project/budget and present at the end which can be critiqued by faculty and students. Also--actually seeing a sample being prepared and injected into a mass spec to determine enrichment would be extremely helpful---possibly a field trip to UAMS (Wolfe Lab) to see setup/demonstration

14. Since my area of research is in protein and amino acids a greater emphasis or longer discussion time on methods, challenges, assumptions, etc. specifically related to protein would have been good.

I did not have a great appreciation for the wide spread usage of isotope tracers in many different areas of study. I do now. Also more confident that the principles learned in my protein research could be applied in a different field of study. The potential areas of postdoc work seem to have opened up substantially.

15. more relevance to clinical studies

16. Practical (dosing, isotope preparation, storage) and regulatory issues related to using stable isotopes in humans and animal studies.

17. I think there are a lot of emerging issues in the kinetic modeling field that are somewhat challenging. Bruce Patterson, Hugh Barrett (or someone like them) could surely speak to the issues.

18. Radioactive tracers personally held little interest for me since I will not be using them. But, there were a lot of people in attendance that did. Plus, it's good to understand in terms of a literature review perspective.

19. I solidified my basic knowledge of tracer techniques, and I became aware of several controversies that I had never considered. I appreciate the emphasis on scientific integrity and proper interpretation of results. Before the course, I particularly wanted to learn about FSR/FBR and A-V balance models to study skeletal muscle. This was covered very well, and it complemented the detailed information in the text.
7. Were the course faculty available and approachable? (Provide best answer)

Not At All 0
Limited 1
Some 3
Substantially 13
Fully 16
Total 32
Skipped 8

8. If you talked to faculty privately, or asked questions after lectures, were discussions or answers helpful? (Provide best answer)

Not At All 0
Limited 0
Some 2
Substantially 15
Fully 13
Total 30
Skipped 10

9. How would you rate the quality and usefulness of the lectures? (Provide best answer)

Poor 0
Good 9
Very Good 6
Excellent 16
Outstanding 2
Total 32
Skipped 8

10. Were the lectures, on average, easy to understand?

Too Easy 0
Slightly Simple 0
Just Right 15
Slightly Hard 15
Too Hard 2
Total 30
Skipped 10

11. Was the homework helpful and appropriate, and did morning problem sessions serve to answer your questions?

Not At All 0
Limited 2
Somewhat 15
<table>
<thead>
<tr>
<th>Likelihood</th>
<th>Count</th>
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<tbody>
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<td>32</td>
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</table>

12. Would you consider returning for this course in the future, or recommending it to students or colleagues?

<table>
<thead>
<tr>
<th>Likelihood</th>
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<tbody>
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<tr>
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</table>
C. Clamping the Conscious Mouse
Annual Course at Vanderbilt University, late summer/early fall

Student Evaluation Summary

These are the results from the evaluations of the 10 students who have taken the annual course each year since its inception.

1. Were all your questions answered to your satisfaction?

<table>
<thead>
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<th>2006</th>
<th>2007</th>
<th>2008</th>
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<td>6</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
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</tr>
<tr>
<td>Below Average</td>
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<td></td>
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</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
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</tbody>
</table>

2. Please, consider the course itinerary; did you feel that sufficient time was offered for each exercise?

<table>
<thead>
<tr>
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<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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<tr>
<td>Superior</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Above Average</td>
<td>6</td>
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<tr>
<td>Poor</td>
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</tbody>
</table>

3. Did you feel that the course material was presented in a clear and concise manner?

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<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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<tr>
<td>Poor</td>
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</table>

4. Were the accommodations adequate for your needs?

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<th>2008</th>
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</tr>
<tr>
<td>Poor</td>
<td></td>
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</tbody>
</table>
5. In thinking of your visit to the Vanderbilt MMPC, how would you rate your overall experience?

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
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<tr>
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</tr>
<tr>
<td>Poor</td>
<td></td>
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</tr>
</tbody>
</table>

*One person and two people did not respond in 2007 and 2008, respectively.*

Please, provide any general comments in the space below:

**Summary of comments (2007 & 2008):**

The most memorable week of my professional career. I was extremely impressed by your diligence towards science, touched by your generosity in sharing the techniques, and overwhelmed by your heartwarming hospitality. I have known about VU-MMPC for years. I used to think that your reputation is simply due to the fact that you guys can handle the “gold standard” techniques, but my experience last week made me realize that your reputation was not simply due to your technical capabilities. Most importantly, it was because David and Owen’s labs have the highest caliber scientists. I came to MMPC to learn the clamp. I think I walked away with things way beyond just the clamp technique. It was an honor to know all of you. You all are a true inspiration.

Great training, exceeded expectations. Loved the hands-on experience. I just wish I had a few more days.

I have nothing but good things to say about this course. I will probably first apply what I’ve learned in the rat, and I feel that I will have no problem in setting up the clamp. The mouse may come later.

Everyone was very helpful, friendly and patient. I really enjoyed the entire experience and appreciate the time everyone took to make the course possible.

The course manual was well prepared and followed what the instructors were discussing. The surgery was tough but the instructors were very helpful in trying to resolve issues.

Thanks to everyone. Everybody has been so helpful and friendly! If possible, if people can have the choice of purchasing the set of necessary instruments in advance (or through the course) that will be great.

Thanks to everyone involved in the clamping course. Every bit of advice, demonstration and smiles has made by experience at Vanderbilt unbelievable. You made the mind-numbing calculation and tedious surgical procedure possible. I can only hope one day, I can pass this forward and give something back to the research community, like you did.

I think more time should be spent on data interpretation with difficult cases. Otherwise, the overall course is really satisfactory.
You provided a great environment to learn these very difficult procedures. It was great to get to know everyone, so when I need some advise while establishing these procedures back at my lab, I can call ore e-mail and associate a face with the person I am contacting. Thanks again.

Free WiFi in the hotel or at Vanderbilt would have been nice. Great mix of surgery and experimental practice combined with rigorous theory. Wonderful course!

Fantastic!! Thank you – no changes I can think of.

I would havee found it helpful to have up front material on doing this in rat. I was able to get the info I needed by asking questions. Also, having the second demo was very helpful. Thank you very much!

Everything is great! Staff are very helpful.