The Case MMPC in its 11th and final year

MMPC Annual Meeting

Bethesda, August 16-17, 2016

Management (1)

- **Director**:

Henri Brunengraber

Dept of Nutrition, CWRU

Pre-clinical metabolic investigations

Use of metabolomics, stable isotopes and mass spectrometry for

flux measurements

pathway discovery

Management (2)

- **Associate Director**:

John Kirwan, PhD

Dept of Physiopathology, Cleveland Clinic

Dept of Nutrition, CWRU

Metabolic investigations in humans and rodents

- Obesity pre- and post-bariatric surgery
- Type 2 diabetes
- Rest and exercise

Management (3)

- **Metabolic Core**
  Colleen Croniger, PhD
  + 2 research assistants

- **Analytical Core**
  Michelle Puchowicz, PhD
  + 2 research assistants

Management (4)

- **Organic Synthesis and Tracers sub-Core**
- Gregory Tochtrop, PhD

  Dept of Chemistry, CWRU

- Synthesis of stable isotopic tracers

Custom-designed isotopic tracers

- Typical custom synthesis: 20 K
- Unaffordable in most cases, but
- Usual cost of labeled synthons: 1 – 3 K
- We can provide MMPC users with customized tracers for 1.5 to 2 times the cost of the synthons.

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- **NB: negative comments from reviewers of our reapplication: “NIH funds should not be used to undermine private industry”**

If so,

THE WHOLE MMPC CONSORTIUM

UNDERMINES PRIVATE INDUSTRY

Our niche

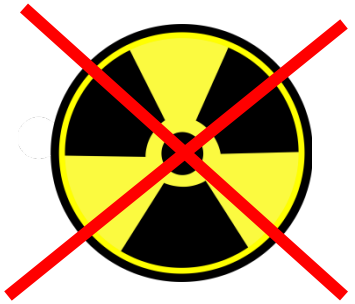
- Measuring metabolic fluxes with stable isotopes
  - lipogenesis
  - protein synthesis
- 50% of Analytical Core business: CoA esters
- Linking stable isotope technology with metabolomics
- Total energy expenditure
  - indirect calorimetry at rest and exercise
  - “doubly-labeled” water

Types of samples handled

- Live rodents mostly from Cleveland area
  - Case
  - Cleveland Clinic
  - University Hospitals
- Frozen tissues shipped from many places by users we trained to run isotopic experiments in their labs
- Some frozen samples from Vandy MMPC

Method development: Radioactivity-free glucose clamping

- *trans*-MMPC project with Vandy, UMass, Yale
- Protocol:
  - infuse [6,6-$^{2}H_{2}$]glucose
  - inject very small bolus of unlabeled 2-deoxyglucose
- All analyses by mass spec
- Planned validation in mice given radioactive + non-radioactive substrates
- Supported by a MicroMouse grant



CoA Esters

- Involved in many reactions
- Present at low concentrations (unstable)
- Many have been unidentified
- Their labeling patterns provide much information on metabolic processes
- Need for methods to detect unknown CoAs
- De-phospho-CoA esters recently identified

Financial constraints

- Many requests for new analytical tests, but
  - each new test requires 1-2 weeks of res. assist. time
  - users refuse to pay for test development
  - small number of samples in new tests
- We must generate 140K/year to be in balance
- Users are tight of money

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- **somehow, we manage!**

Kiss of death of Case MMPC

- Reviewers felt that, with the development of isotopic techniques at Vandy, the Case MMPC was no longer needed:
- *“With Vanderbilt MMPC moving towards adding Metablic Flux Analysis to their service list, the demand for similar services at this Case core during the next funding cycle may be impacted”.*
- *“The core complements other centers, but how does the activity fit with the new sub-core ofMetabolic Flux Analysis at Vanderbilt?”*

Upcoming changes in the MMPC Consortium

- No more ^{13}C-NMR (Yale)
- >80% decrease in mass spec assays and in stable isotopic labeling patterns (Yale, Case)
- No more assays of lipogenesis and protein synthesis by the $^{2}H_2O$ method (Case)
- No more CoA esters assays (Case, Yale)
- >80% decrease in long-distance training of users in stable isotopic techniques for
  - flux measurements
  - mechanistic investigations

The Yale MMPC should have been kept

- Only one to run both ^{13}C-NMR and mass spec
- Developed MIMOSA software that correlates positional and mass isotopomer analyses
- Most important development in stable isotopic techniques in 20 years
- NB: metabolomics of microbiome without carbon and nitrogen tracing has low potential for discovery


Did you hear, Hans?
Yes Bernie, I just turned over!
B.R. LANDAU
H.A. KREBS

Planning the transition year

- How do we inform and re-direct our users?
- Can some techniques be transferred from Yale and Case to the other MMPCs?
- Plan transition(s) in the Isotope Course
- Suggestion to NIDDK: as done in the past, recruit MBA students to
  - do a market analysis of the new MMPC Consortium
  - assess the impact of the new changes
  - recommend adaptive actions




We remain part of the MMPC family!

So long Folks!