Scientific Need

1. More communication between “complication-specific” communities
2. New and better animal models for diabetic complications

NIH Response

Interdisciplinary consortium to develop multiple new animal models that closely mimic the human complications of diabetes for studying disease pathogenesis, prevention and treatment.

- Thirteen **Pathobiology Sites** design and study animal models of complications
- Close partnership with the **Jackson Laboratories (JAX)** and the **Mouse Metabolic Phenotyping Centers (MMPCs)** to ensure that all interesting models are screened across multiple complications

  Hypothesis: *common pathways of disease are involved in multiple complications; so a good model of one complication may prove to be a good model of another.*

- All data and resources go to **Coordinating and Bioinformatics Unit (CBU)**

AMDCC Principal Investigators and Programs

Diabetic Nephropathy

Erwin Bottinger, Mount Sinai SM

Role and Mechanisms of Epithelial Injury in Diabetic Nephropathy

Frank Brosius, Univ of Michigan

Recapitulating Transcriptional Pathways of Human Diabetic Nephropathy in Mice

Thomas Coffman, Duke University

Angiogenic Signals in Diabetic Complications

Raymond Harris, Vanderbilt

Generating Mouse Mutants with Diabetic Nephropathy

Moshe Levi, Univ of Colorado

Novel Models of Diabetic Nephropathy

Kumar Sharma, UCSD

Adiponectin and Nox 4 in Diabetic Kidney Disease

Oliver Smithies, UNC-Chapel Hill

Bradykinin, NO and Mitochondrial DNA Damage in Diabetic Complications

Diabetic CV Disease

E. Dale Abel, Univ of Utah

Modeling Diabetic Cardiomyopathy and Microangiopathy

Richard Davis, UCLA

Atherosclerosis/other Complications in Hyperlipidemic BKS Diabetic Mouse

Ira Goldberg & Ed Fisher, Columbia

Creating Glucose Responsive Cardio-vascular Complications

Nobuyo Maeda, UNC-Chapel Hill

Dyslipidemia, Lipoic Acid and Diabetic Vascular Complications in Mice

Diabetic Neuropathy

Eva Feldman, Univ of Michigan

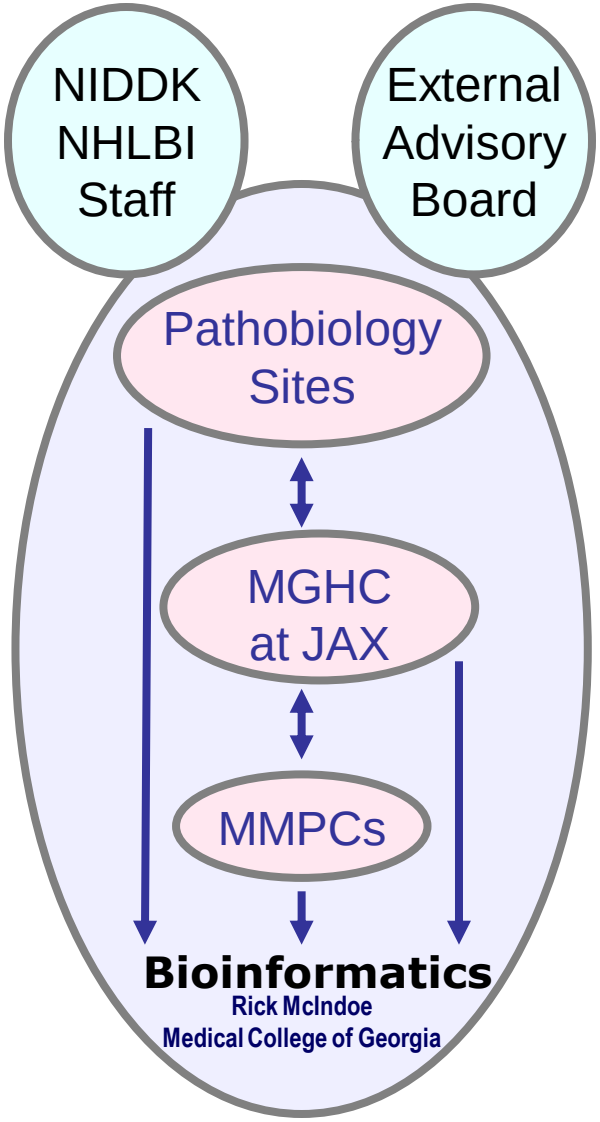
Mitochondrial SOD as a Target for Diabetic Neuropathy

Diabetic Uropathy

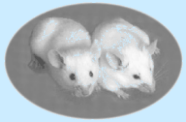
Firouz Daneshgari, Case Western

Diabetic Uropathy Pathobiology Site

AMDCC Structure



AMDCC Partners



Type 1 Diabetes Resource at the Jackson Laboratories

The AMDCC supports a Mouse Generation and Husbandry Core at the NIH-sponsored Type 1 Diabetes Resource at the Jackson Labs (T1DR-MGHC) to assist with model development and phenotype characterization under controlled conditions.

http://type1diabetes.jax.org/

Mouse Metabolic Phenotyping Centers

The AMDCC collaborates with the NIH-sponsored MMPCs to phenotype mice for diabetic nephropathy, neuropathy, retinopathy and cardio-vascular disease. The MMPCs work to improve public access to a wide range of existing tests. They also support a P&F program to develop new technologies for phenotyping animal models of complications.

www.MMPC.org

Pilot & Feasibility Program

Applications due May 1

Up to $100K total costs for 1 yr

The AMDCC funds Pilot and Feasibility projects each year to advance the mission of the consortium. Areas of scientific emphasis for the program vary from year to year.

A request for applications is issued each February. Full details at:

www.amdcc.org/shared/pilotFeasibility.aspx

Available Resources

The AMDCC generates several resources (models, data, protocols, tissue samples, histological slides, validation criteria, publications, etc.) that are available to all through our Coordinating and Bioinformatics Unit (CBU) at www.AMDCC.org.

The AMDCC is supported by

NIDDK National Institute of Diabetes and Digestive and Kidney Diseases

National Heart Lung and Blood Institute

National Institutes of Health

Animal Models of Diabetic Complications Consortium

AMDCC
THE ANIMAL MODELS OF DIABETIC COMPLICATIONS CONSORTIUM

The **AMDCC** is an 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

www.AMDCC.org

AMDCC Program Staff

Chris Ketchum (NIDDK)

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Cristina Rabadan-Diehl (NHLBI)

JDRF

Barbara Araneo

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AMDCC EAB

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Jeffrey Kopp (NIH)

John Sedor (Case Western)

Juergen Naggert (Jackson Labs)

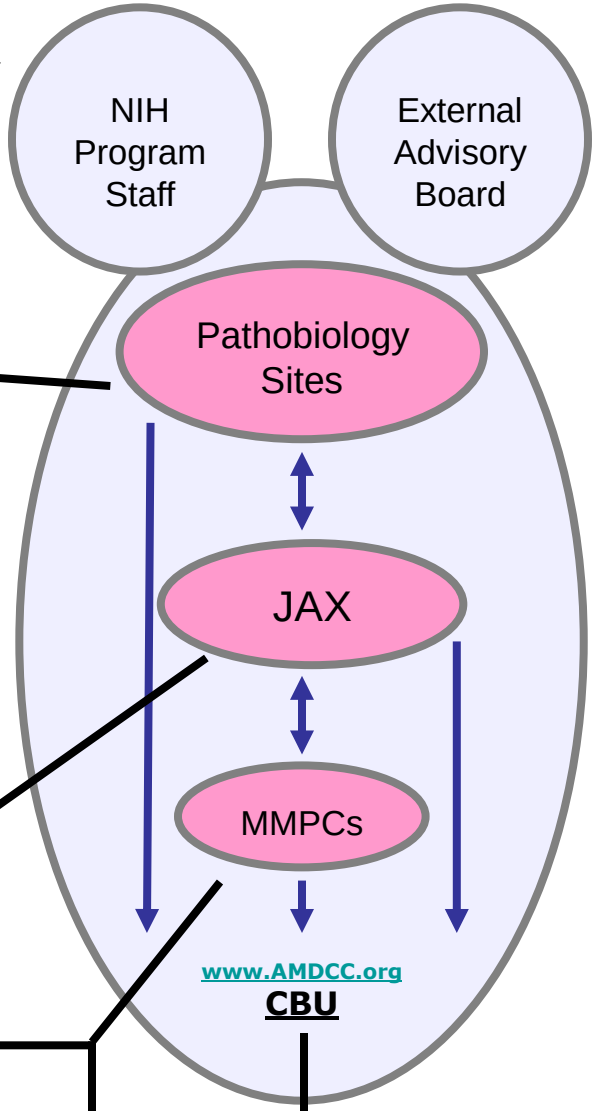
Phil Tsao (Stanford Univ)

Doug Zochodne (U of Calgary)

Lynn Hedrick (Scripps)

AMDCC Pathobiology Site PIs

1. Eva Feldman (U of Mich) – ***CHAIR***
2. Dale Abel (Univ of Utah)
3. Erwin Bottinger (Mount Sinai SOM)
4. Chip Brosius (Univ of Mich)
5. Tom Coffman (Duke Univ)
6. Firouz Daneshgari (Case Western)
7. Richard Davis (UCLA)
8. Kumar Sharma (UCSD)
9. Ira Goldberg (Columbia Univ)
10. Ray Harris (Vanderbilt Univ)
11. Moshe Levi (Univ of Colorado)
12. Nobuyo Maeda (UNC)
13. Oliver Smithies (UNC)



AMDCC P&F Awardees

1. Steven Abcouwer (Penn St)
2. Alistair Barber (Penn St)
3. Thomas Baumann (Univ of Oregon)
4. Bruce Berkowitz (Wayne State)
5. Vivek Bhalla (Stanford Univ)
6. Lori Birder (Univ of Pitt)
7. Wade Bushman (Univ of Wisc)
8. Nigel Calcutt (UCSD)
9. Katherine Dell (Case Western)
10. Paul Dolber (Duke Univ)
11. Matthew Fraser (Duke Univ)
12. Geoffrey Gurtner (Stanford Univ)
13. John Iacomini (Brigham & Womens)
14. Matthias Kretzler (Univ of Mich)
15. Ruth Ley (Cornell Univ)
16. Carmella Molina (IUPUI)
17. Thomas Neuberger (Penn St)
18. Aria Olumi (MGH)
19. Jean Schaffer (Wash Univ)
20. Leonard Shultz (JAX)
21. Young-sup Yoon (Emory Univ)
22. Karl Zuzak (UT Arlington)

AMDCC MGHC

Ed Leiter

Racheal Wallace

MMPC PIs

Renee Leboeuf (Univ of Wash)

Charlie Alpers (Univ of Wash)

David Wasserman (Vanderbilt Univ)

AMDCC-MMPC CBU PI

Rick McIndoe (MCG)

AMDCC Accomplishments

1. Added >20 PIs to the consortium through our P&F program, primarily in the fields of retinopathy, neuropathy, uropathy, stems cells, microbiome, etc.

2. Generated ~40 animal models that mimic various aspects of the human complications of diabetes, many of which are freely available from JAX.

3. Published >180 papers, including both high impact original publications and “consortial” reviews.

4. Published ~60 standardized laboratory protocols and validation criteria on the AMDCC website, ensuring that data can be easily compared between members of the consortium and the outside community.

This cycle of the AMDCC ends in the summer of 2011

What we don’t know: **T1D $**

What we may know: **NIDDK $**

2011 Trans-NIDDK Initiative

Diabetic Complications Consortium (formerly the AMDCC)

Purpose: Given the strong evidence that diabetic complications are linked via dysregulation of common pathways, there is a need to facilitate the sharing of ideas, information, and reagents between research communities investigating similar pathologic mechanisms in different organs.

Background: One of the greatest strengths of the AMDCC has been its ability to create an environment where communication and collaboration is fostered between investigators that don't typically interact. Continuing to provide such an environment remains a high priority.

Research Goals and Objectives: Solicit new collaborative activities that would shift the current focus on model development and candidate-gene approaches toward systems-biology approaches. These might include:

1. Application of stem cells, including induced pluripotent stem (iPS) cells and regenerative therapies to the repair and reversal of diabetic complications.
2. Assessment of multiple complications in model systems (C.elegans, zebrafish, drosophila, etc).
3. Testing the role of genes or loci that arise from ongoing human genetics/sequencing efforts.
4. Use of relevant model systems to accelerate gene X environment (GEI) studies.
5. Interrogation of existing clinical samples or resources with DNA analysis, omics, histology, and pathology as well as looking for circulating blood and urine biomarkers.
6. Collaborations with existing NIH supported PPGs, Centers, Cores, CTSAs, etc.
7. Inclusion of other co-morbidities of diabetes and obesity including non alcoholic fatty liver disease, gastrointestinal complications, peripheral vascular disease, and wound healing.

Mechanism:

- Coordinating and Bioinformatics Unit (CBU)
- Pilot and Feasibility program
- Annual Diabetic Complications Scientific meeting

Proposed Duration: 5 years

Agenda

- Discuss existing resources for complications research
- Discuss future opportunities in complications research

Goal

- Position the community to capitalize on available resources and opportunities in 2011 and beyond

Follow-up

- Publish our deliberations on the AMDCC website
- Invite public input, discussion and feedback

Animal Models of Diabetic Complications Consortium

Steering Committee Meeting

Admiral Fell Inn, Baltimore, MD

Given the strong evidence that diabetic complications are linked via dysregulation of common pathways, there is a need to facilitate the sharing of ideas, information and reagents between research communities investigating similar pathologic mechanisms in different organs.

August 4, 2010 (Wednesday)

5:00	**Introductions**	Chris Ketchum
5:15	**T1D Rapid Access to Intervention Development** http://www.t1diabetes.nih.gov/T1D-RAID/	Myrlene Staten
5:45	**T1D Preclinical Testing Program** http://www.t1diabetes.nih.gov/T1D-PTP/	Nigel Calcutt
6:15	**International Mouse Phenotyping Consortium** http://www.nature.com/news/2010/100525/full/465410a.html?s=news_rss	Mark Moore
6:45	**NIA Resources/Phenome Database** http://www.nia.nih.gov/ResearchInformation/ScientificResources/	Nancy Nadon
7:15	**JDRF Programs and GoKIND Samples** http://www.jdrf.org/	Barbara Araneo
7:45	**Adjourn**	

August 5, 2010 (Thursday)

8:00	**Introductions**	Chris Ketchum
8:15	**Jax Phenotyping and Resources**	Ed Leiter
9:15	**AMDCC Website as a Resource**	Rick McIndoe

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9:45	**Break**	
10:00	**Future Opportunities**	Eva Feldman

The AMDCC Steering Committee (SC) has identified the following research opportunities. The chair of each **Discussion Group** will provide a 10-15 min overview to address **Discussion Question 1** and set the stage for each group to address **Discussion Questions 2-7**. Please feel free to self-select your group, with the goal of having roughly equal representation in each.

Discussion Groups

1. **Regeneration and Repair (Moshe Levi):** Application of regenerative medicine to the repair and reversal of diabetic complications, including stem cells and induced pluripotent stem (iPS) cells in the treatment of complications.

2. **Pathways and Models (Ray Harris):** Development of novel experimental model systems to assess multiple complications, including addressing the utility of using worms, fish and flies, and if these models are suitable for addressing both the pathogenesis of complications as well as providing novel tools for therapy screening.

3. **Genetics and Epigenetics (Tom Coffman):** Application of genetic and epigenetic studies and technologies to examine complications. Expand our genetic understanding of complications by identifying the genetic basis of disease susceptibility across mouse strains and using relevant model systems to accelerate gene X environment (GEI) studies.

4. **Systems Biology (Chip Brosius):** Application of transcriptomics, proteomics, metabolomics and lipidomics across models and between models and humans for phenotyping multiple pathways. Combine these approaches with other systems biology approaches such as miRNA to identify the most attractive pathways and networks for study and assess their potential as therapeutic targets.

Discussion Questions

1. What is the current status of the area in terms of basic, translational and clinical research with regards to all diabetic complications?

2. What is the potential impact of these studies on the field of complications research? Is there sufficient and meaningful significance to the idea/approach to move the field of complications research forward?

3. Are there technical or scientific barriers preventing progress in the area?

4. Are there clear objectives that can be outlined for this area which, if achieved, will enhance our understanding and treatment of complications? Are there existing human samples or resources with DNA analysis, omics, histology and pathology that could be utilized to help achieve these goals?

5. Can this area identify new circulating blood and urine biomarkers?

6. Can existing NIH resources be leveraged to address these questions? Can partnering with existing NIH supported CTSAs, PPGs, Centers or ongoing technology driven cores to better phenotype progressive disease across models provide assistance to this area of research? Would this be useful to advance the field forward?

7. Can this area of research assist our understanding of all diabetic complications (including other co-morbidities such as non alcoholic fatty liver disease, peritonitis, gastrointestinal complications, peripheral vascular disease, etc)?

12:00	**Lunch**	
1:30	**Group Reports**	Group Chairs
3:30	**Consortial Discussion**	Eva Feldman
4:00	**Steering Committee Adjourn**	
5:00	**EAC Meeting Adjourn**	