AMDCC

THE ANIMAL MODELS OF DIABETIC COMPLICATIONS CONSORITUM

www.amdcc.org

# How to Build a Mouse Model: Animal Models of Diabetic Complications Consortium (AMDCC)

- AMDCC:  What is it?
- Better strategy to address complex genetic diseases?
- Mice as models: What we know at this point
- Focus: Nephropathy

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# Animal Models of Diabetic Complications Consortium

MAIN | DATA SEARCH | DATA ANALYSIS | ABOUT AMDCC | CONTACT | MEMBER AREA

## Steering Committee

The AMDCC Steering Committee is the governing body of the consortium. Members of the commitee develop the scientific goals of the consortium, create the necessary subcommittees and oversee the implimentation of the consortiums activities.

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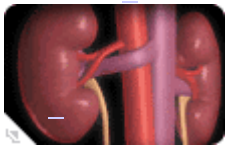

## Nephropathy Committee

The AMDCC Nephropathy Committee develops strategies for creating and analyzing mouse models of diabetic complications of the kidney.

Validation criteria:
View in pdf or html

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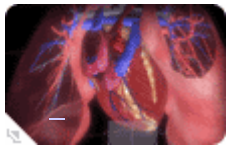

## Cardiovascular Committee

The AMDCC Cardiovascular Committee develops strategies for creating and analyzing mouse models of diabetic complications of the heart and vascular systems.

Validation criteria:
View in pdf or html

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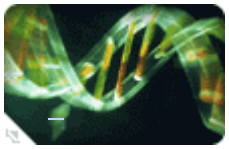

## Bioinformatics

The AMDCC Bioinformatics Committee develops the strategies for data sharing and data analysis among the consortium members.

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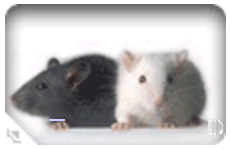

## Animal Husbandry

The AMDCC Animal Husbandry Committee advises on the standard operating procedures for housing and maintaining the animal models developed by the consortium.

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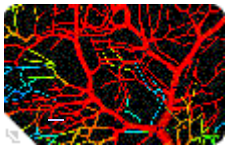

## Neuropathy Committee

The AMDCC Neuropathy Committee works on the strategies for creating and analyzing mouse models of diabetic complications of the neuro.

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## Retinopathy Committee

The AMDCC Retinopathy Committee develops strategies for creating and analyzing mouse models of diabetic complications of the retino.

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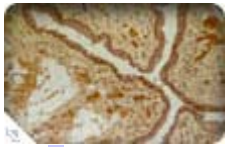

## Uropathy Committee

The AMDCC Uropathy Committee works on the strategies for creating and analyzing mouse models of diabetic complication of the uro.

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## Ontology Workgroup

The AMDCC Ontology Committee works on developing controlled vocabularies used in the data storage scheme.

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## External Advisory Panel

The AMDCC External Advisory Panel is made of experienced investigators in the fields of diabetes, kidney pathologies, cardiovascular disease, animal models, animal phenotyping and bioinformatics. This group of outstanding scientists provide insite and guidance to the Steering Committee.

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NIDDK National Heart, Lung and Blood Institute | Department of Health and Human Services | National Institutes of Health

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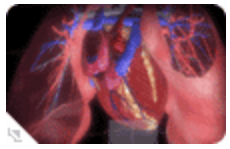
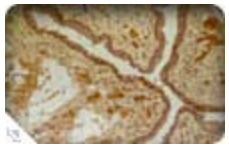
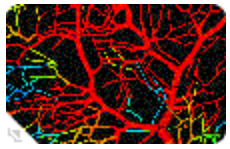
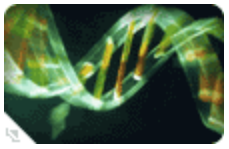
# Animal Models of Diabetic Complications Projects

| AMDCC Principal Investigator | Participating Institution | Area |
|---|---|---|
| Erwin Bottinger | Albert Einstein College of Medicine | Nephropathy |
| Jan Breslow | Rockefeller University | Cardiovascular |
| Matthew Breyer | Vanderbilt University | Nephropathy |
| Frank Brosius | University of Michigan | Nephropathy and Neuropathy |
| David Clemmons | University of North Carolina | Cardiovascular |
| Thomas Coffman | Duke University Medical Center | Nephropathy and Cardiovascular |
| Firouz Daneshgari | The Cleveland Clinic Foundation | Uropathy |
| Willa Hsueh | University of California Los Angeles | Cardiovascular |
| Donald Mclain | University of Utah | Cardiovascular |
| Richard McIndoe | Medical College Of Georgia | Bioinformatics |

NIH (NIDDK, NHLBI), JDRF sponsored

NIDDK

Department of Health and Human Services

NATIONAL INSTITUTES OF HEALTH

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# Animal Models of Diabetic Complications Projects

- Consortium premise: Current animal models do not adequately reproduce human diabetic complications
- Goal:  Develop animal models with human diabetic complications in order to better test mechanisms of disease and therapeutic interventions.

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# Current models do not reproduce human diabetic complications

- **Areas where current mouse models fall short**
  - Renal failure
    - At present no mouse model of diabetes develops renal failure
    - Albuminuria
      - no benchmarks for the amount of albuminuria reflective of glomerular disease
      - only modest increases in proteinuria detected in present models (at most ten fold whereas renal disease in man is associated with a 100-1000 fold increase in albuminuria)
  - Pathological changes are not robust: absence of wide-spread mesangial sclerosis, kimmelstiel Wilson nodules, arteriolar hyalinosis or tubulointerstitial fibrosis

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# Animal Models of Diabetic Complications Nephropathy Criteria

- Albuminuria at least 10x and preferably 100x normal levels
- Diffuse or nodular glomerular sclerosis ± arteriolar hyalinosis. Ultimately, interstitial fibrosis.
- Decline in renal function to <50% of control levels

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# Strategy: Common Protocols



## Protocol for Albuwell M kit: Murine Microalbuminuria ELISA By Exocell Inc

Version: 1
Replaced by version: N/A
Edited by: Kathi Burke (Frank Brosius Lab)



**Summary:** Albuwell M is an indirect competitive ELISA designed to monitor kidney function in the mouse by measurement of urinary albumin. To complete the assay, sample and rabbit anti-murine albumin antibody are added to albumin coated wells. The antibody interacts and binds with the albumin immobilized to the stationary phase or with albumin in the fluid phase, hence the notion of competitive binding.

A subsequent reaction with anti-rabbit -HRP conjugate labels the probe with enzyme. After washing, only the antibody-conjugate bound to the stationary phase remains in the well, and this is detected using a chromogenic reaction. Color intensity is inversely proportional to the logarithm of albumin in the fluid phase. The assay may be completed in less than 2.5 hours..



## Low-Dose Streptozotocin Induction Protocol (Mouse)

Version: 1
Replaced by version: N/A
Edited by: The University of Michigan Medical Center , Frank Brosius



**Summary:** This protocol is used by AMDCC members to induce diabetes in a number of the animal models developed by the consortium. This induction protocol is used to induce a diabetes similar to a type I diabetic.

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# Strategy: Complementary models and sharing

- Listing of all models on web site; semiannual group presentations
- Cooperative development of models
- Sharing of models for different phenotyping
- Common database
- Publication review

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# Current Models

| Animal model | Background strain | current status | Phenotyping (begin-end) | Consortium collaborators |
|---|---|---|---|---|
| | | | | |
| SOD2 (+/-) STZ | c57Bl6 | final phenotyping | 3-02 to 8-03 | |
| db/db | c57Bl6 | breeding pairs | NA-breeding stock | |
| SOD2 (+/-) db/db | c57Bl6 | first litters 4 wks old | 5-03 to 12-03 | |
| GLUT4 (-/-) STZ | c57Bl6 | phenotyping ongoing | 11-01 to 12-03 | Einstein |
| GLUT4 (-/-) db/db | c57Bl6 | breeding starting | 11-03 to 10-04 | Einstein |
| GCLC (+/-) STZ | c57Bl6 | GCLC colony expansion | 6-03 to 5-04 | |
| GCLC (+/-) db/db | c57Bl6 | GCLC colony expansion | 7-03 to 6-04 | |
| fyn (-/-) | mixed | phenotyping complete | | |
| fyn (-/-) STZ | 129S | embryonic rederivation | 6-03 to 5-04 | |
| fyn (-/-) db/db | 129S | embryonic rederivation | 9-03 to 12-04 | |
| GLUT1 tg STZ | c57Bl6 | characterizing multiple GLUT1tg lines | 8-03 to 11-04 | Hopkins |
| GLUT1 tg db/db | c57Bl6 | characterizing multiple GLUT1tg lines | 10-03 to 1-05 | Hopkins |
| podocin cre x flox SOD2 | c57Bl6 | breeding currently | 6-03 to 3-04 | Vanderbilt |
| podocin cre x flox GLUT4 | c57Bl6 | breeding currently | 4-03 to 2-04 | Utah |
| podocin cre x flox PPARg | c57Bl6 | breeding currently | 4-03 to 2-04 | UCLA, Vanderbilt |
| conditional podocin cre | c57Bl6 | characterizing multiple lines | NA-breeding stock | |
| synapsin cre (neuron specific) | c57Bl6 | crossing with Rosa26 | NA-breeding stock | |
| nestin cre (neuron specific) | c57Bl6 | crossing with Rosa26 | NA-breeding stock | |

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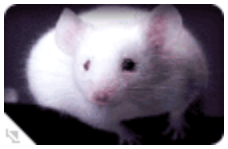
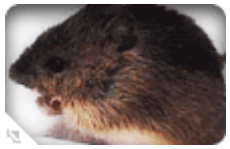
# Strategy: Oversight, data sharing and database management

## DATA SUBMISSION

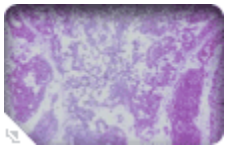
Animal Models Database | Phenotype Experiment Database | Histology Database | Member Information



Submit Model/strain
Add or edit an animal model or strain



Submit Experiment
Add or edit phentotype assay experiment data.



Submit Histology
Upload histology images and provide pathology reports for the slides.

Submit Institution Information
Add institution-specific information, such as MTAs, to the system.

Submit Publication
Submit a new publication for review by the Publications Committee.

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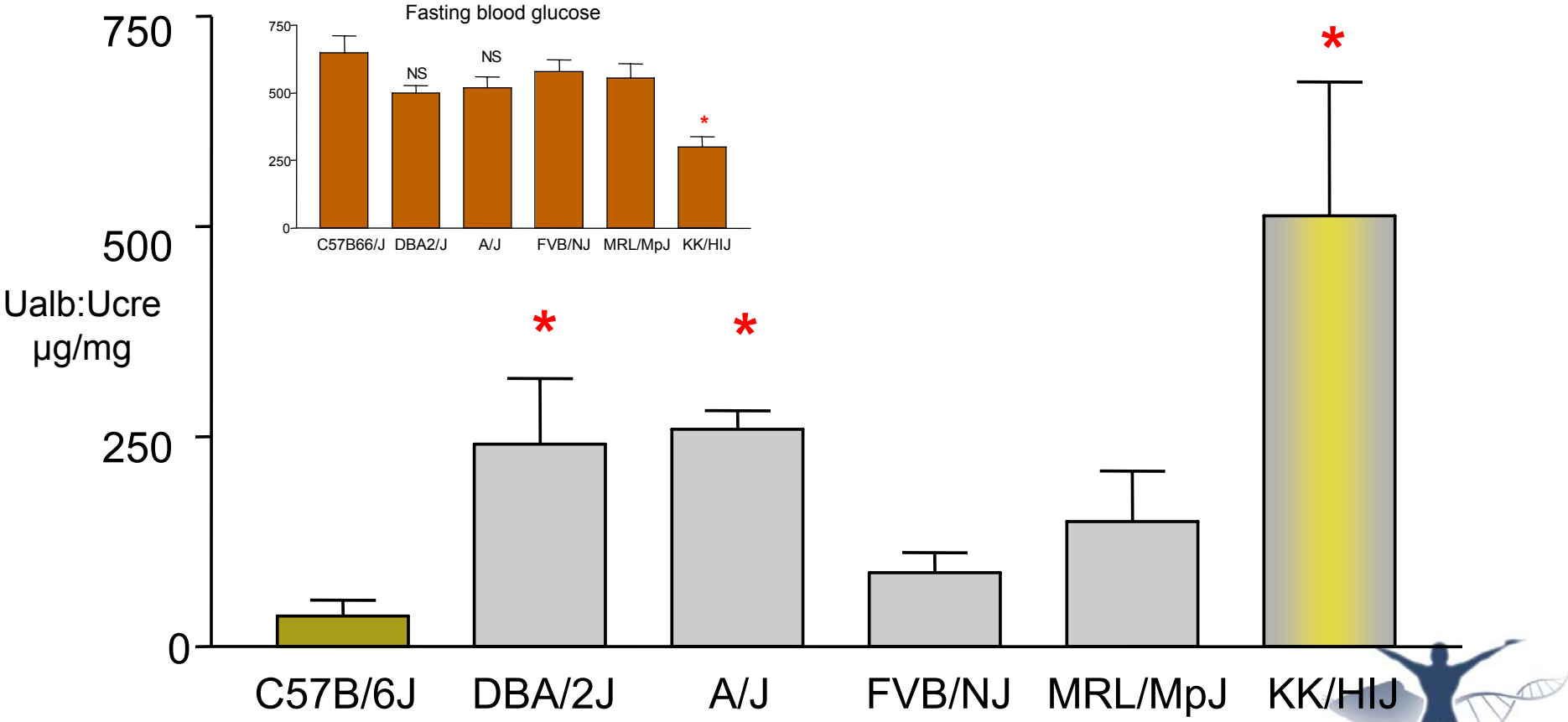
# Differences in Diabetic Renal injury in different mouse strains




**Breyer et al.**

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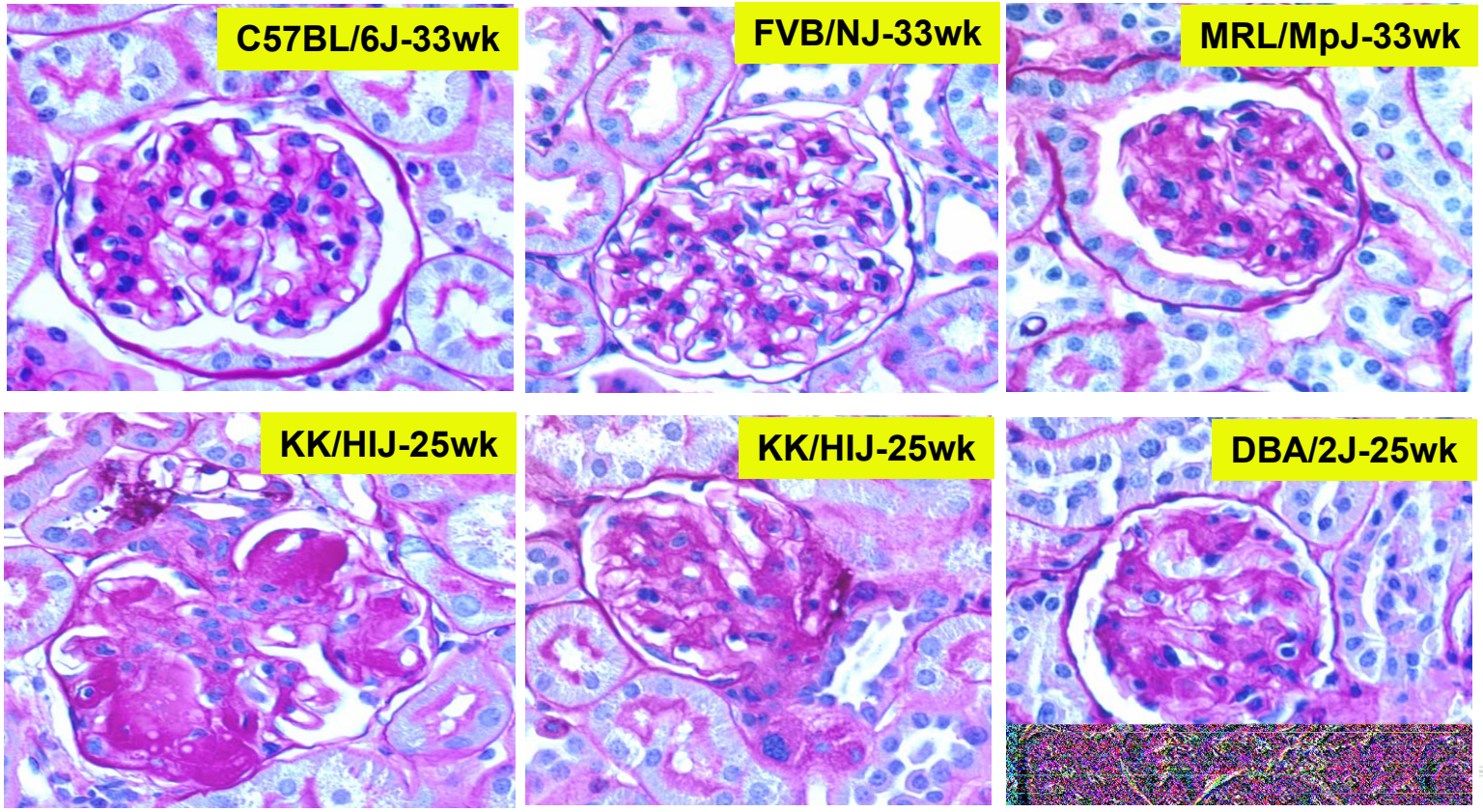
# Heterogeneity of diabetic kidney disease in mice




Breyer et al.

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# AMDCC-YEAR 2

- Established common protocols and phenotyping tools that are successful and reproducible
- Confirmed and further characterized mouse strain differences in diabetic complications
- Made advances in establishing more human-like models of diabetic complications
- Created a user-friendly web-based data entry and communication tool
- Established a true consortium approach

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Thank you to:
Dr. Starr
Dr. Briggs

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