Animal Models of Diabetic Complications Consortium
(U01 DK076134-01)

Annual Report
(2007)

"Novel Models of Diabetic Nephropathy"
University of Colorado at Denver Health Sciences Center

Principal Investigator
Moshe Levi

Address: 4200 East 9th Avenue, BRB 451, Denver, Colorado 80262
Phone: 303-315-1898
E-mail: Moshe.Levi@UCHSC.edu

Table of Contents

		Page
Part A:	**Principal Investigator's Summary**	**3**
1.	**Project Accomplishments (2007)**	**4-5**
2.	**Collaboration**	**5**
3.	**Address previous EAC comments**	**NOT APPLICABLE**
4.	**Publications**	**6**
Part B:	**Individual Project Reports By Responsible Investigator (if applicable)**	**N/A**

Animal Models of Diabetic Complications Consortium
(U01 DK076134-01)

Part A:

Principal Investigator's Summary

1. Program Accomplishments:

Hypothesis

Our hypothesis is that FXR deletion, especially in genetically susceptible mice, will confer increased susceptibility to diabetic nephropathy through its coordinated effects on lipid metabolism, oxidative stress, AGEs/RAGE, proinflammatory cytokines and fibrosis inducing growth factors. We propose that targeted deletion of FXR will enhance diabetic nephropathy in mouse models of a) type 1 diabetes mellitus (OVE26), b) diet induced obesity and insulin resistance, and c) type 2 diabetes mellitus (db/db). In contrast, FXR overexpression will markedly limit or prevent diabetic nephropathy in OVE26 and db/db mice.

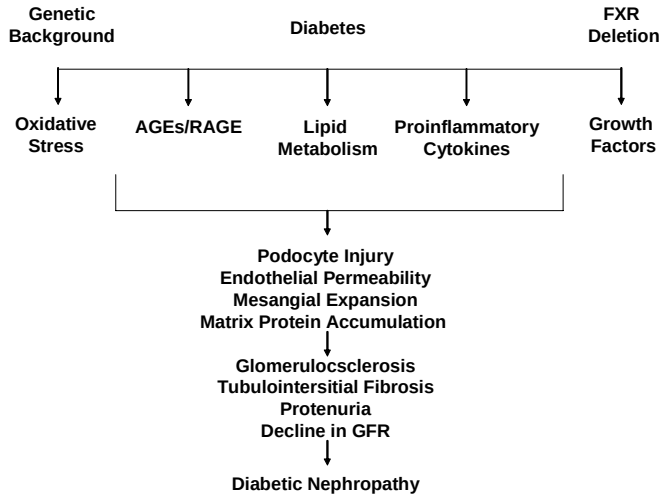

Figure 1: Our hypothesis indicating that in diabetes mellitus FXR as a function of genetic background plays a critical role in the pathogenesis of diabetic nephropathy by modulating lipid metabolism, oxidative stress, AGEs/RAGE, proinflammatory cytokines, and fibrosis inducing growth factors.

Recent Progress and Major Accomplishments

In a recent study (Diabetes in press: manuscript attached) we have demonstrated that a) in mice with diet induced obesity and insulin resistance and b) in db-db mice with type 2 diabetes mellitus FXR agonists markedly attenuate proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis. These protective actions are accompanied by prevention of lipid accumulation, expression of profibrotic growth factors, proinflammatory cytokines, and oxidative stress. Furthermore these effects of FXR are seen in mesangial cells grown in culture in a high glucose environment where treatment with FXR agonists or molecular overexpression of FXR prevent the high glucose induced lipid accumulation, increased expression of profibrotic growth factors and proinflammatory cytokines, indicating that the in vivo protective actions of the FXR agonists is mediated in part by direct effects on the kidney.

This study provides the rationale for generating FXR KO mice which we expect will accelerate diabetic nephropathy in mouse models of type 1 diabetes (Akita or OVE26) or type 2 diabetes (db/db mice).

This study also provides the rationale for generating FXR transgenic mice which we expect will significantly prevent or attenuate diabetic nephropathy in mouse models of type 1 diabetes (Akita or OVE26) or type 2 diabetes (db/db mice).

Plans for the Upcoming Year

In collaboration with AMDCC and Jackson Labs generate 1) FXR KO mice on the FVB and DBA genetic backgrounds and 2) db/db mice on the FVB genetic background.

Preliminary Milestones for 2009 and Beyond

The generation of FXR KO mice on the FVB and DBA genetic backgrounds is in progress: these mice will be cross bred with type 1 (Akita or OVE26) and type 2 (db/db) mice on the same genetic background.

2. Collaboration:

With other AMDCC PIs: Have been interacting with other AMDCC investigators regarding the identification of the best renal proximal tubular Cre mice.

With JAX: 1) Generating FXR KO mice on the FVB and DBA genetic backgrounds; 2) determining whether NON mice, compared to C57Bl/6 mice, is a better model for diet induced obesity and insulin resistance; 3) determining whether NONcNZO mice, compared to db/db mice, is a better model of type 2 diabetic nephropathy.

With the MMPCs: Collaborating with Seattle MMPC for histology services and measurement of serum creatinine by HPLC

With other non-AMDCC PIs: With Streamson Chua for the generation of FVB db/db mice; with Streamson Chua and Jeffrey Kopp for the generation of FXR KO and FXR Transgenic mice

3. Address previous EAC comments:

NOT APPLICABLE THIS YEAR

4. Publications:

1. Proctor G, Jiang T, Iwahashi M, Wang Z, Li J and Levi M: Regulation of Renal Lipid Metabolism, Lipid Accumulation, and Fibrosis in Akita and OVE26 Mice with Type 1 Diabetes. Diabetes 55: 2502-2509, 2006
2. Levi M: Do Statins have a beneficial effect on the kidney? Nature Clinical Practice Nephrology: 2: 666-667, 2006
3. Lanaspa MA, Giral H, Breusegem SY, Halaihel N, Baile G, Catalan J, Carrodeuga JA, Barry NP, Levi M, and Sorribas V: Interaction of MAP17 with NHERF3/4 induces translocation of the renal type IIa Na/Pi transporter to the trans-Golgi. American Journal of Physiology: Renal Physiology 292: F230-F242, 2007
4. Villa-Bellosta R, Bogaert YE, Levi M, Sorribas V: Characterization of Phosphate transport in rat vascular smooth muscle cells: Implications for vascular calcification: ATVB 27: 1030-6, 2007
5. Wang C, Sorribas V, Sharma G, Levi M, Draznin B: Insulin attenuates vascular smooth muscle calcification but increases vascular smooth muscle cell phosphate transport: Atherosclerosis, in press.
6. Jiang T, Wang XX, Scherzer P, Wilson P, Tallman J, Takahashi H, Li J, Iwahashi M, Sutherland E, Arend L, and Levi M: FXR Modulates Renal Lipid Metabolism and Fibrosis and Diabetic Nephropathy: Diabetes: in press
7. Bauer T, Reusch J, Levi M, Regensteiner J: Skeletal Muscle Deoxygenation Following the onset of moderate exercise suggests slowed microvascular blood flow kinetics in type 2 Diabetes: Diabetes Care: in press