Diabetic Complications Consortium

Application Title: Clinical Development of Hydroxy-propyl beta cyclodextrin in Diabetic Kidney Disease

Principal Investigator: Alessia Fornoni MD PhD

1. Project Accomplishments:

We have successfully completed aim 1 of the application and demonstrated that low dose CD administered subcutaneously to diabetic mice protects from the development of albuminuria and improves serum creatinine. This is an extremely important finding, as this dose is translatable to application in humans and will increase the likelihood of a clinical development of CD. The FDA will be approached to obtain an IND for the use of CD in DKD.
Aim 2 was not completed because the drug administered orally to mice was not tolerated because of gastrointestinal side effects (diarrhea). However, data obtained from this experiment will also guide the future clinical development of CD as a drug that will need to be administered subcutaneously.

2. Specific Aims:

We tested the hypothesis that low dose CD protects podocytes in DKD.
We had proposed the following specific aims:
Specific Aim 1-Determine the effects of low dose subcutaneous CD on cholesterol accumulation in podocytes, and its impact on podocyte injury in one experimental model of T2D.
We will use animal models of T2D and human podocytes cultured in the presence of the sera of patients with T2D (n=40) enrolled in existing research cohorts to test the following hypotheses:

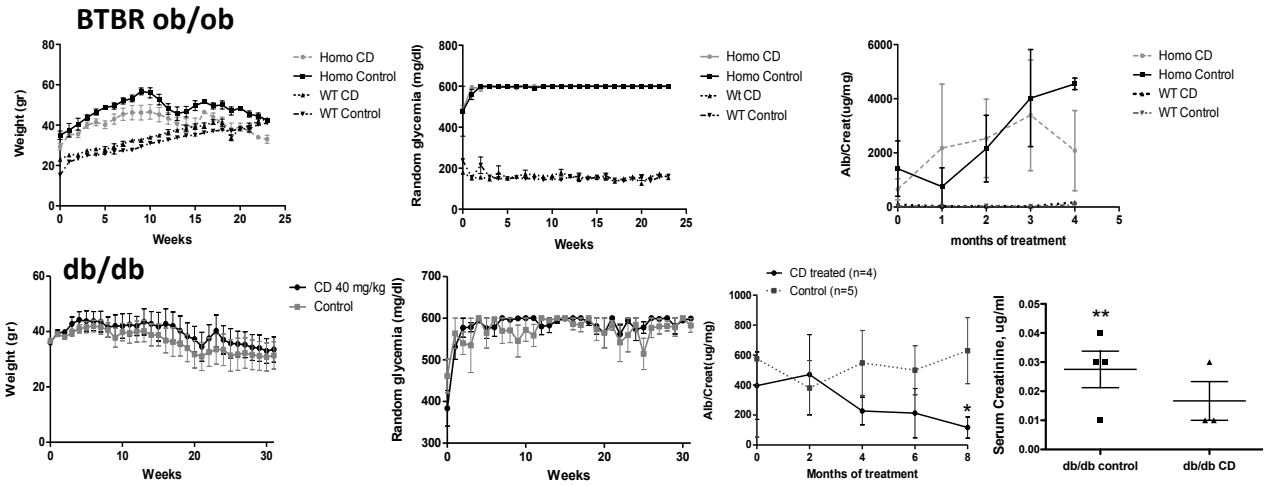
a) CD treatment of BTBR *ob/ob* (T2D) mice at 40 mg/kg/day preserves podocyte function and prevents the development of proteinuria when compared with vehicle treated mice.
b) Treatment with CD in cultured podocytes exposed to the sera of patients with DKD directly causes cholesterol efflux and protect from apoptosis.

Preliminary data supporting this aim are: i) Treatment of human podocytes with the sera of patients with DKD in vitro induces cholesterol-dependent actin remodeling and apoptosis that can be prevented by CD; ii) treatment of BTBR ob/ob mice with high-dose CD reduces albuminuria and mesangial expansion. iii) low dose CD reduces albuminuria in a pilot study in db/db mice.

Results

We have observed that low dose CD (40 mg/kg) in BTBR ob/ob mice had a non-significant protection from DKD. However, the colony of BTBR ob/ob mice was characterized by a high incidence of skin and visceral organ tumors. As we though this

may have a confounding effect in our experiments, we have repeated a low dose CD experiment in db/db mice and demonstrated that CD improves albuminuria and creatinine in db/db mice as demonstrated below.



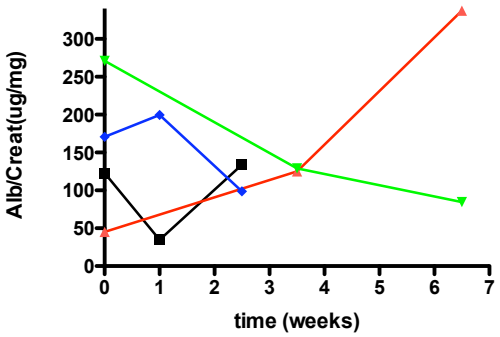
Specific Aim 2-Determine if low dose CD administered orally has a similar effect on macroalbuminuria of CD administered subcutaneously.

Based on the experimental data available in the drug master file for Hydroxy-propyl-beta cyclodextrin provided by Johnson & Johnson under confidentiality agreement, we will test the following hypothesis:

Oral administration of CD at 40 mg/kg/day is well tolerated and is as effective as subcutaneous CD in reducing microalbuminuria in BTBR ob/ob mice.

Results

CD was discontinued in all mice except in one out of 4 because of steatorrhea. It is unclear at this point why one mouse was able to tolerate PO CD better than others. Urine collected from this mouse (red line below), however, demonstrated worsening albuminuria over time when compared to three control mice (green, blue and black). Decision was made not to pursue the oral administration of the drug, at least in diabetic mice.



3. Publications (related to this Pilot Project):

Fornoni A, Merscher S, Kopp JB. Lipid biology of the podocyte: new perspectives offer new opportunities. Nature Review Nephrology, 10:379-88, 2014.

Coward R, Fornoni A. Insulin signaling: implications for podocyte biology in diabetic kidney disease. Curr Opin Nephrol Hypertens, 24:104-10, 2015.

Mitrofanova A, Wahl P, Morales X, Correa M, Pedigo C, Ducasa GM, Burke G, Merscher S, Fornoni A. Cyclodextrin Protects Podocytes in Focal Segmental Glomerulosclerosis. 2015. Kern Lipid Conference, Vail, CO. Poster Presentation

Mitrofanova A, Correa M, Morales X, Pedigo C, Ducasa GM, Burke G, Merscher S, Fornoni A. Podocyte Sphingomyelin Phosphodiesterase Acid Like 3b (SMPDL3b) Expression Correlates with GFR in Diabetic Kidney Disease. European Diabetic Nephropathy Study Group. Oral Presentation.

Pedigo CE, Leclercq F, Correa-Medina M., Mitrofanova A., Mendez A., Nelson R., Burke GW, Fornoni A, Merscher S. TNFa Alters Cholesterol Homeostasis Leading to Podocyte Apoptosis in Diabetic Kidney Disease. 2015. Center for Translational Science Institute Conference. Miami, FL.

Pedigo CE, Leclercq F, Correa-Medina M., Mitrofanova A., Mendez A., Nelson R., Burke GW, Fornoni A, Merscher S. Altered Cholesterol Homeostasis Causes Podocyte Apoptosis in Diabetic Kidney Disease. NYAS Diabetic Kidney Disease: Drug Discovery and Clinical Development Challenges. 2014. New York, NY. Travel Award

Pedigo CE, Leclercq F, Correa-Medina M, Mitrofanova A, Mendez A, Nelson R, Burke GW, Fornoni A., Merscher S. Attenuated Cholesterol Efflux Causes Podocyte Cholesterol Accumulation and Apoptosis in Diabetic Kidney Disease. ASN Kidney Week. 2014. Philadelphia, PA. Oral presentation

Mitrofanova A, Morales X, Pedigo CE, Villarreal R, Correa-Medina M, Burke GW, Merscher S, Fornoni A. Sphingomyelin-Phosphodiesterase-Acid-Like-3b Affects Insulin Signaling in Podocytes. ASN Kidney Week. 2014. Philadelphia, PA. Poster Presentation

Correa-Medina M, Rampersaud E, Pedigo C, Nair V, Morales XA, Kretzler M, Nelson RG, Merscher S and Fornoni A. Personalized podocyte biology for the prediction of diabetic kidney disease. American Society of Nephrology (ASN) meeting; Philadelphia, PA. 2014, Poster presentation.

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