Symposium Speakers

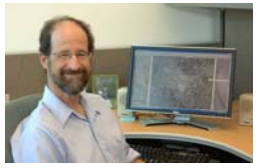
Eric Wallace, MD-UAB

Melanie Sivley, OD—UAB

Peter Harris, PhD-Mayo Clinic

Michal Mrug, MD-UAB

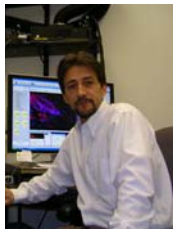
Thomas Natoli, PhD—Genzyme Corporation



Robert Weiss, MD-UCD

Welcome Presenters

Anupam Agarwal, MD-UAB



Brad Yoder, PhD-UAB

Summary & Conclusions

Presenter

David G. Warnock, MD-UAB

UAB MEDICINE/NEPHROLOGY

MINI-SYMPOSIUM ON FABRY DISEASE AND POLYCYSTIC KIDNEY DISEASE PROSPECTS FOR IMPROVED CARE

Tuesday
November 18, 2014
10:00 AM
FINLEY COMPASS BANK CONFERENCE CENTER
(behind the Kaul Human Genetics Building)
Birmingham, Alabama 35294

UAB
MEDICINE/NEPHROLGY

Box lunch will be provided to registrants: Contact Katrina Moore to register for lunch and the symposium by

Thursday, November 13, 2014

krmoore@uab.edu or 975-7583

Program Overview

OBJECTIVES

a) Review the current unmet needs in the treatment of Fabry disease

b) Review the current unmet needs in the treatment of Autosomal Dominant Polycystic Kidney Disease

FABRY & POLYCYSTIC KIDNEY DISEASE

c) Review the animal mode of polycystic kidney disease

d) Review the metabolomics pathways and mechanisms of action of inhibitors of glucosylceramide synthase.

Expected Improvements and Increase in Knowledge.

Through expert presentations, interactions, discussions, the following expectations will be realized

a) Enhance communications and understanding of the basic cellular mechanisms involved in glucosylceramide synthase inhibition will promote collaborations, and research projects that will bridge the knowledge gaps that currently exist

b) Enhanced communications and understanding of the unmet clinical needs in Fabry Disease and polycystic kidney disease will promote collaborations and clinical initiatives that will further the understanding and treatment options for patients with Fabry nephropathy and patients with autosomal dominant polycystic kidney disease

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AGENDA

10:00 AM Welcome

Anupam Agarwal, MD—Director of Nephrology and the UAB/UCSD O'Brien Core Center for Acute Kidney Injury Research

Brad Yoder, PhD—Director, Hepato/Renal Fibrocystic Diseases Core Center

10:15 AM Fabry Disease; 10 years of Enzyme Replacement Therapy (ERT) and the Current Unmet Clinical Needs

Eric Wallace, MD-UAB

10:45 AM Novel Ocular Findings in Classically Affected Male Fabry Patients After Long-Term ERT

Melanie Sivley, OD—UAB

11:15 AM "ADPKD Genetic Complexity, and Expermental Therapies"

Peter Harris, PhD—Mayo Clinic

12:00 NOON Networking Lunch

12:30 PM Mouse Models of Polycystic Kidney Disease

Michal Mrug, MD—UAB

1:15 PM "Glycosphingolipid Dysregulation in Cystic Kidney Disease"

Thomas Natoli, PhD—Genzyme Corporation

2:00 PM Metabolomics Analyses in Renal Cystic Disease

Robert Weiss, MD—UCD

2:45 PM Summary and Conclusions; Quo Vadis?

David G. Warnock, MD-UAB

3:00 PM Open Discussion

3:30 PM Adjourn

Background Information

Agalsidase-beta is currently available for the treatment of Fabry disease in the US, and clinical experience with enzyme replacement therapy (ERT) has accumulated with its use since its approval in April 2003. There is a significant reduction in severe target organ events (kidney, heart, brain) with ERT after an initial treatment period of approximately 6 months (lag time to benefit). (1) Longer-term results have shown a marked reduction in progression to end-stage renal disease; hence, the natural history of Fabry disease has been changed, at least for males with non-sense mutations (classic phenotypes).

The efficacy of ERT is reflected in the clearance of endothelial GL3 deposits, (2) for which the product is licensed in the US for treating Fabry disease. Lysosomal storage diseases are currently treated with enzyme replacement therapy and more recently with small molecules that inhibit glucosylceramide synthase and reduce the concentration of the proximate substrate in the gangliocerebroside pathway (3) Analogues have been designed that cross the blood-brain barrier and are not excreted from neuronal cells through the MDR1 pathway. (4) Members of this class of small molecules are referred to as substrate reduction therapy (SRT), and have recently been approved by the FDA for treatment of type 1 Gaucher disease. A member of this same class of small molecules (GZ40 2671) is currently undergoing clinical testing in male patients with Fabry disease (Clinicaltrials.gov NCT02228460).

An intriguing connection has appeared between the lysosomal storage diseases and polycystic kidney disease. Natoli et al have reported than inhibition of glucosylceramide synthase activity ameliorates the cyst phenotype in mouse models of polycystic kidney disease. (5,6) There is para-pelvic cystic phenotype described in Fabry disease, (7,8) but not in Gaucher disease. The mTOR signaling pathway is important in polycystic kidney disease, (9) as well as controlling basic cellular functions like autophagy that are most prominent in terminally differentiated cells like podocytes, cardiomyocytes, and neurons. (10-12)

This background material highlights the knowledge gaps that exist and are obstacles to the design and execution of definitive clinical trials of SRT in both lysosomal storage diseases and polycystic kidney disease. The major unmet clinical need in Fabry disease is providing effective, bioavailable therapy for involvement of podocytes, cardiomyocytes and neurons. These cells determine the long term outcomes for renal, cardiac, and central nervous system involvement in Fabry disease, and may be more amenable to systemic therapy with oral agents than the currently available intravenously ERT.

References:

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6. Natoli TA, Smith LA, Rogers KA, et al. Nat Med 2010; 16:788-92.
7. Glass RB, Astrin KH, Norton KL, et al. Fabry Disease: J Comput Assist Tomogr 2004;28:158-68.
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11. Grahammer F, Wanner N, Huber TB Nephrol Dial Transplant 2014;29 Suppl 1:i9-i18.
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