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

Symposium Speakers

Melanie Sivley, OD—UAB
Anupam Agarwal, MD-UAB
Brad Yoder, PhD-UAB

Welcome Presenters

David G. Warnock, MD-UAB

Summary & Conclusions

Presenter

Peter Harris, PhD-Mayo Clinic
Michal Mrug, MD-UAB
Thomas Natoli, PhD—Genzyme Corporation
Robert Weiss, MD-UCD

UAB MEDICINE/NEPHROLOGY

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

c) Review the animal mode of poly cystic kidney disease

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

POLYCYSTIC KIDNEY DISEASE

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 poly cystic 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

*Supported by an unrestricted educational grant from Genzyme Corporation. Sponsored by the Nephrology and Research and Training Center the O'Brien Center for Acute Kidney Injury Research (P30 DK073337) and the Hepato/Renal Fibrocystic Diseases Core Center (P30 DK074038). CME accreditation through the NRTC (RSS-14938)

The University of Alabama School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The University of Alabama School of Medicine designates this Regularly Scheduled Series a maximum of 1 AMA PRA Category 1 credits/ME. Physicians should claim only the credit commensurate with the extent of their participation in the activity. The University Of Alabama School Of Medicine is an equal opportunity/affirmative action.

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 (2420 2671) is currently undergoing clinical testing in male patients with Fabry disease (Dincaurin.org/NCIT0228460).

An intriguing connection has appeared between the lysosomal storage diseases and polycystic kidney disease. Natali et al have reported that 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 intraveneously ERT.

References: