K30 monthly meeting: intro

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Clinical background

- B.S., biological sciences, Stanford University
- M.D., UCLA School of Medicine
- Internship, pediatrics, Cedars-Sinai Medical Center (CSMC)
- Residency, pediatrics and general genetics, CSMC
- Research fellow, biochemical genetics, CSMC
Why genetics?

- Not just the study of the very rare
- Newborn screening data indicating that some genetic disorders are more common than previously indicated
- Study of the “extreme outliers” give insight into pathogenesis of more common diseases
  - rMED, COL9, and osteoarthritis
  - OI, COL1, and osteoporosis
  - AIDS resistance, CCR9, and HIV infection
- Need for translational research
  - Just because it’s rare doesn’t mean there is no need to develop and test treatments
Research background

- Basic science
  - *in vitro* models of protein (co)localization
  - analysis of anaphase checkpoint proteins
  - Genome-wide linkage analysis

- Clinical science
  - Fabry disease
  - Natural history description
  - Oral chaperone clinical trial
Fabry Disease Background

- **Inheritance**: “X-linked recessive disorder that affects males; females unaffected”

- **Etiology**: deficiency of _-galactosidase

- **Function**: degradation of glycosphingolipids

- **Pathophysiology**: glycosphingolipid accumulation in tissues, especially the vascular endothelium

GL₃ / globotriaosylceramide

Lactosylceramide

_-galactosidase
Clinical Manifestations of Fabry Disease

- **CNS / PNS (Cognitive function preserved)**
  - Stroke
  - Acroparesthesias ("Burning sensation of the hands and feet")
  - Anhidrosis / hypohidrosis with subsequent heat intolerance
  - Decreased vibration sense

- **Pulmonary**
  - Small-airway infiltration
  - Abnormal gas exchange

- **Cardiac**
  - Microvascular myocardial ischemia
  - Conduction abnormalities
  - Valvular insufficiency
  - Concentric, non-obstructive left ventricular hypertrophy

- **Renal**
  - Proteinuria / microalbuminuria
  - Progressive loss of GFR → renal failure

From Warnock, 2005
From Seino, 2005
From Whybra, 2001
Why study Fabry disease?

- It’s more common than previously indicated
  - Published population freq ~ 1:30,000
  - Newborn screening freq ~ 1:3,300

- To gain insight into disease pathogenesis
  - Stroke, myocardial ischemia, and peripheral neuropathy are common (esp DM)

- To find better treatment
  - “Enzyme replacement therapy” with IV recombinant α-galactosidase FDA-approved in 2004
  - Slows progression of GFR loss
  - ERT does not adequately treat or reduce stroke risk, peripheral neuropathy, or cardiomyopathy
Fellowship research aims

- To further characterize the natural history and response to therapy of Fabry disease in females
  - Retrospective chart review has been conducted
  - Results compiled and analyzed
  - Manuscript written and accepted for publication

- To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of an oral medication, AT1001, in patients with selected missense mutations in \(-\text{Gal A}
  - Prospective, open-label, phase I/II clinical trial
  - Enrollment ongoing
Any questions? 😊

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- Fellowship funded by the American College of Medical Genetics Foundation / Genzyme Corporation Fellowship in Biochemical Genetics
- Genzyme Corporation had no role in the conception, design, execution, or publication of the results of this project
- Own no shares of the Genzyme corporation but am a private shareholder of Biomarin pharmaceuticals