Establishing Evidence for Treatments of (ultra)Rare Diseases

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Inborn Errors of Metabolism

- Rare
  - PKU 1:10.000 Newborns
  - 40 / year in Canada
  - 4 / Year in BC
- Ultrarare
  - AGAT Deficiency
  - First described 2001
  - 10 patients / 4 families worldwide

Systematic Literature Review "treatable ID"*

- Identify all IEMs
  - presenting with ID / DD as predominant feature
  - for which causal treatment is available
- Characterize causal treatments and effects on ID and related morbidity
- Describe levels of evidence for these treatments

* Clara van Karnebeek and Sylvia Stockler, manuscript in preparation

Results

- 75 treatable ID
- Comorbidities
  - Neurologic
  - Behavior, psychiatric
  - Systemic
- Treatments
  - Diet, dietary supplements
  - Vitamins, cofactors
  - HSCT
  - pharmacological

Evidence vs Clinical Practice

Evidence*	N=disorders	Clinical practice
1b, 1c Individual RCTs, "all or nothing"	4	
2a,b,c Cohort studies (systematic review or individual) Outcome Research	13	
3 Case control (systematic review or individual)		
4 Case series	55	36 (65%)
5 Expert opinion, bench research, proof of principle	5	

*Oxford Center for EBM, 2009

Example Evidence Level 4

Lack of EBM in IEM

- Newly discovered > 1970
- Extremely small patient cohorts
- Treatments based on pathophysiological understanding
- Treatments “learning by doing”
- No legislation for diets and nutritional supplements

Lorenzo's Oil for X-ALD

- X-ALD: neurodegenerative disorder, onset childhood, accumulation of VLCFA
- GTE/GTE (Lorenzo's oil) inhibits endogenous VLCFA synthesis (1980ies)
- Research funded and initiated by Lorenzo's parents
- Lorenzo's oil = nutritional supplement
- Available for everyone
- Hugo Moser: international observational study
- Still no clear evidence

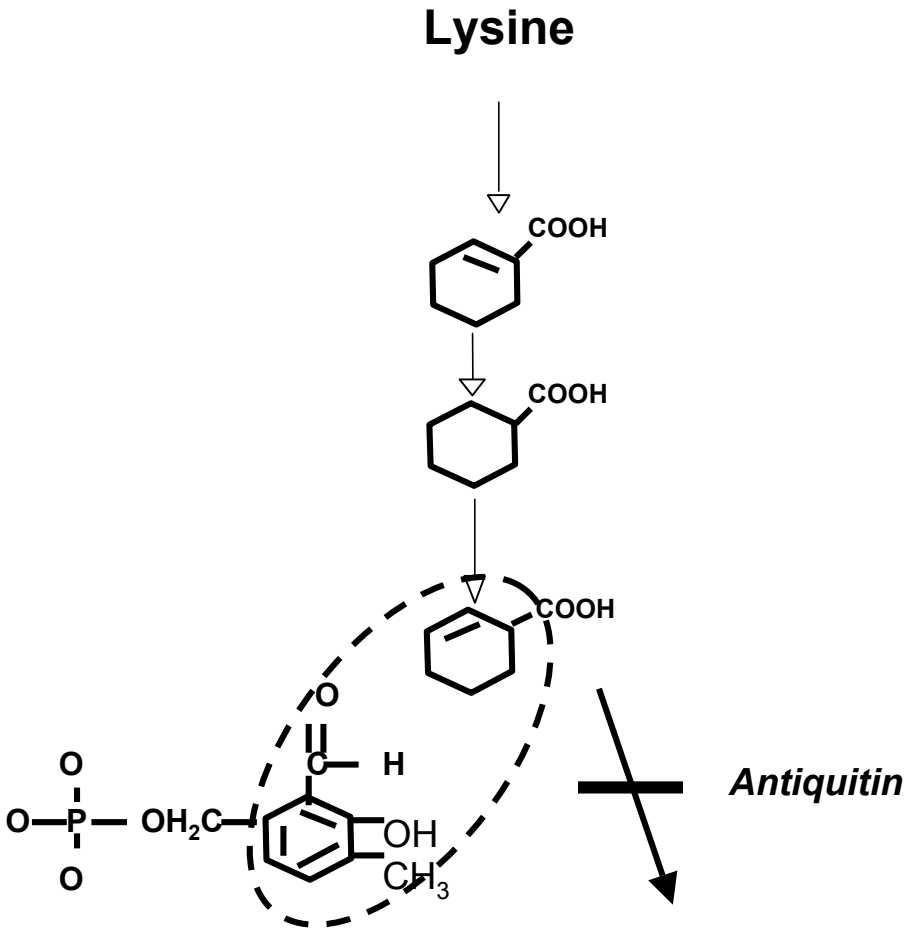
>2011: New Opportunities

- International databases
- Natural history studies
- Expensive treatments: evidence prerequisite for funding
- New methodologies
- Unethical not to establish evidence

PDE / Antiquitin Deficiency

- Intractable neonatal epileptic encephalopathy
- Seizures responsive to vitamin B6 (pyridoxine)
- Reason for vitamin B6 responsiveness not known
- Despite seizure control with vitamin B6, ID

2006: Genetic Defect in PDE: *Antiquitin Deficiency*



PDE / ATQ deficiency =
Cerebral organic aciduria
Comparable to GA!

Mills et al Nature Medicine 2006

Opportunity: systematic approach to lysine restricted diet in PDE/ATQ def

- Known since 1954
- Established patient cohorts
- Single case study: n=2
  - proved reduction, normalization of biomarkers
  - Improved behavior after 2 weeks

Treatable Intellectual Disability Endeavour in BC (TIDE-BC)

- BCCH Collaborative Area of Innovation
- 2.25 million dollar for 3-5 years

- 1) Implementation of a protocol for diagnostic work up of patients with ID with treatable IDs as a priority
- 2) Establishing evidence for treatments of rare IEMs (eg PDE/ATQ deficiency)

Planning an International Trial for treatment of PDE/ATQ deficiency with lysine restricted diet.

- RCT? Diet not accepted by some families
- Observational study
- Outcomes?
- Funding
- Regulations
- Workshop at SSIEM Meeting Genva Sept 2011