



## A research update from the Fridovich-Keil lab



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\*no conflicts of interest to disclose

### In the next 45 minutes...

- BIG picture of where we have been and where we are going in galactosemia research
- Brief updates on three projects:
  - Ovarian function in galactosemia
  - Scholastic outcomes in galactosemia
  - What have we learned from the flies and what does it mean for people?

### Want to hear more about galactosemia research from "team Emory"?

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**Friday 2:15-3:15pm:**

- Ovarian function in galactosemia (Fridovich-Keil)
- Movement Disorders 101 (Testa)

**Saturday 10-11am:**

- Galactosemia Research: finally flying forward (Fridovich-Keil)
- How to help your child learn (Taddeo)

**Saturday 11:15am-12:15pm:**

- POI and fertility in galactosemia (Spencer and Badik)
- Scholastic and behavioral issues (Fridovich-Keil and E. Ryan)

**Saturday 3-4pm:**

- How to help your child learn (Taddeo)



### Galactosemia research in the Fridovich-Keil lab: BIG picture

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*"We want to understand what causes the acute and long-term complications experienced by people with galactosemia so we can do something positive about it."*

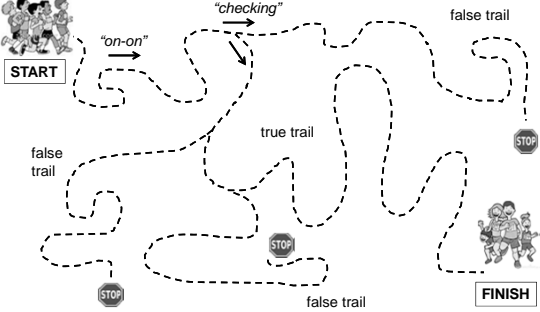
### Our approaches then and now...

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- a yeast model system to distinguish mild from severe mutations in human *GALT*
- search for modifiers of outcome in patients (ovarian, scholastic, neurological, growth...)
- a whole animal genetic model (*fruit fly*) to
  - test candidate genetic and environmental modifiers
  - screen for new and unexpected modifiers of outcome
  - test potential interventions
- connecting the dots from mutation to biochemical and metabolic defect, to acute and long-term outcome, to effective intervention

### Why galactosemia research is like hashing\*...



\* a group running activity originated in 1938 by British colonial officials and expatriates living in Kuala Lumpur, Malaysia

update on:

## ovarian function in galactosemia

**Old news:** >80% of girls and women with classic galactosemia experience POI

**Questions:**

- when/where does the problem occur?
- biomarkers of ovarian function?
- mechanism?

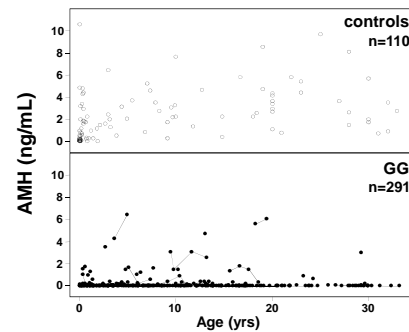
**Goals:**

- accurate prognosis
- safe and effective intervention



ovarian function in galactosemia:

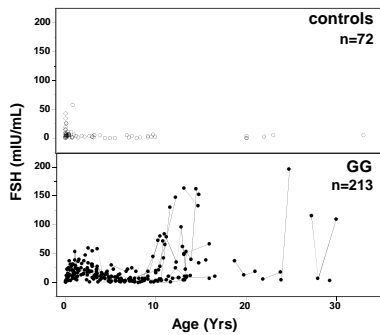
When does the problem occur? How do we know?



Spencer, Badik, et al. in preparation

ovarian function in galactosemia:

What can we learn from FSH?



Spencer, Badik, et al. in preparation

ovarian function in galactosemia:

Is predicted residual GALT activity a prognostic indicator of outcome?

Some GALT alleles with residual activity detected in yeast

S135L  
D136H  
D98N  
D197G

L195P  
P183T  
A78T  
Y209C

Some GALT alleles with no residual activity detected in yeast

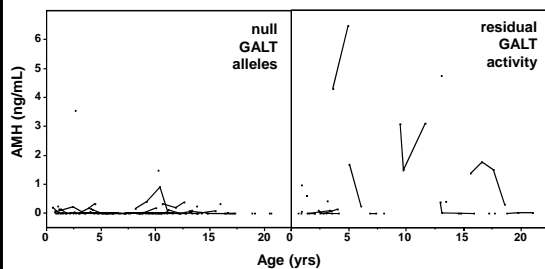
Q188R  
F171S  
D98H  
M142K

R204X  
Q206R  
R148P  
5kb del

Gleason et al. in preparation

ovarian function in galactosemia:

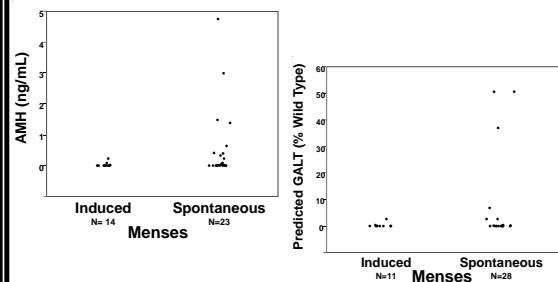
GALT activity influences biomarkers



Spencer, Badik, et al. in preparation

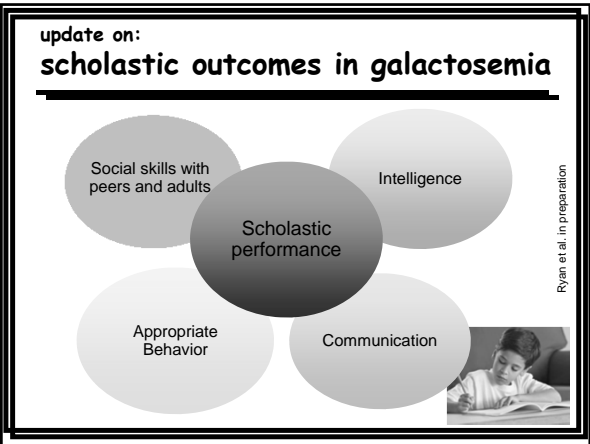
ovarian function in galactosemia:

Predictors of spontaneous menses

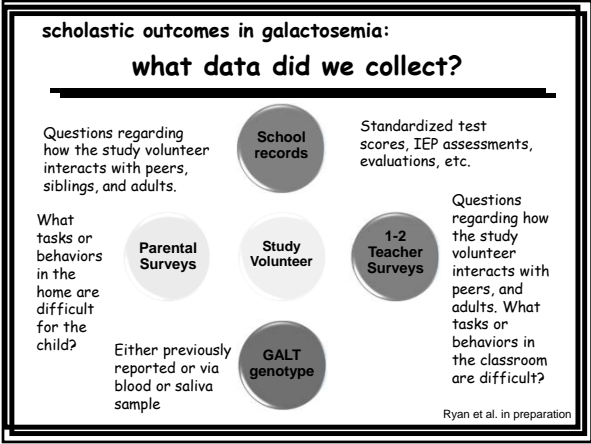
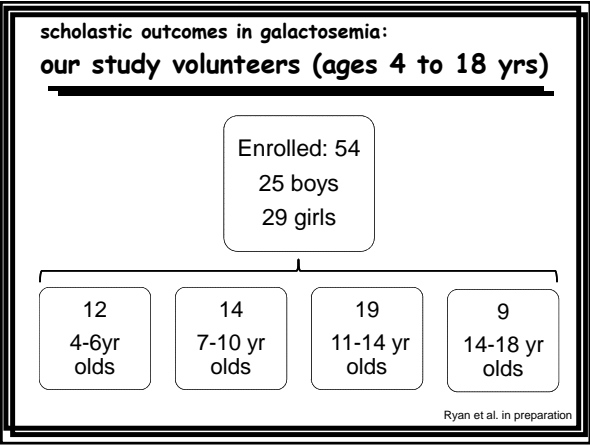


Spencer, Badik, et al. in preparation

**What does this tell us about mechanism, and what does it mean for girls and women with classic galactosemia?**



- scholastic outcomes in galactosemia:  
from previous reports we know...**
- range of IQ but average is below normal
  - higher than normal incidence of depression
  - speech difficulties common
  - anecdotal evidence of difficulty in school
    - does this reflect a cognitive problem?
    - is this secondary to a speech problem?
    - other options....



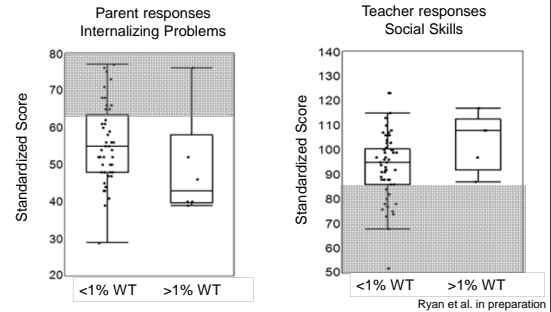
- scholastic outcomes in galactosemia:  
results...**
- about half of the children in each age group were achieving below grade level
  - about half were receiving some kind of special educational services
  - most common behavioral problems reflected "internalizing" behaviors and difficulty with social skills
- Ryan et al. in preparation

**scholastic outcomes in galactosemia:  
Is residual GALT activity a prognostic indicator?**

Predicted GALT activity (as a % of wild-type level)	0-1%	>1%
Overall (n=53)	47	6
Enrolled in special education (n=17)	15	2
Not enrolled in special education (n=15)	12	3
Achieving in Math (n=16)	11	5
Not Achieving in Math (n=19)	18	1
Achieving in Language Arts (n=18)	13	5
Not Achieving in Language Arts (n=17)	16	1

Ryan et al. in preparation

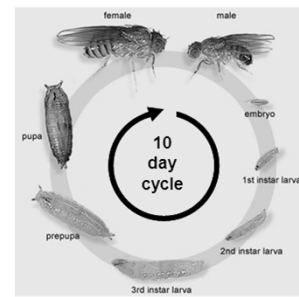
**scholastic outcomes in galactosemia:  
Is residual GALT activity a prognostic indicator?**



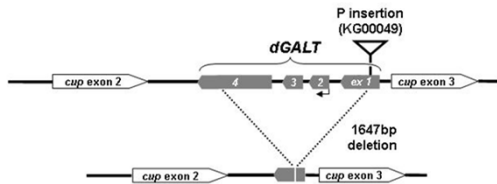
Ryan et al. in preparation

**What does this tell us  
about mechanism, and  
what does it mean for  
children with classic  
galactosemia?**

**What have we learned from the flies  
and what does it mean for people?**



**Deleting fly GALT**

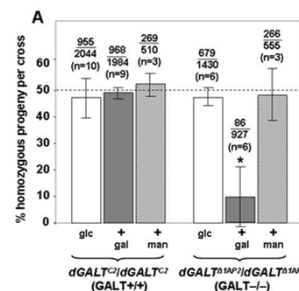


**Imprecise excision (*dGALT*<sup>Δ1AP2</sup> and *dGALT*<sup>Δ2V2</sup>) junction sequences:**

...GTGCCAAACTCAAACCTAAACcatgatgaataaa GGAAATAGTCTAATACGACT...

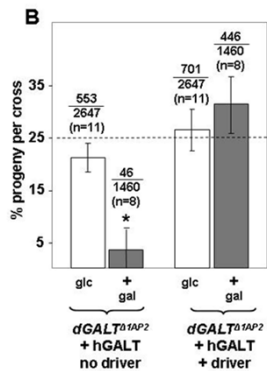
Kushner et al (2010) DMM

**GALT-deficient *Drosophila*  
are galactose-sensitive**



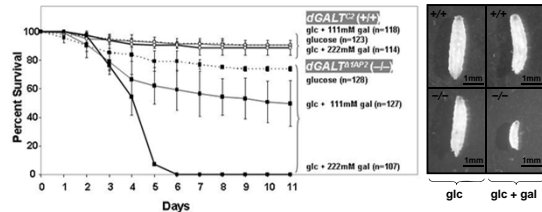
Kushner et al (2010) DMM

**GALT-deficient *Drosophila* are rescued by expression of human GALT**



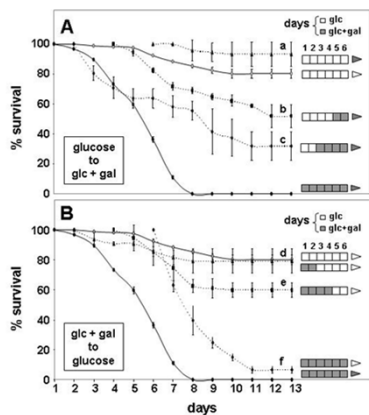
Kushner et al (2010) DMM

**GALT-deficient *Drosophila* die as larvae when exposed to galactose**



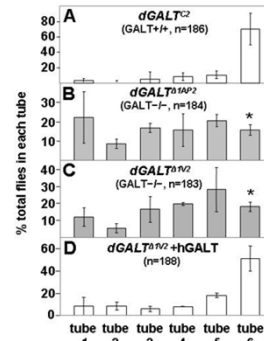
Kushner et al (2010) DMM

**Impact of dietary galactose exposure**



Kushner et al (2010) DMM

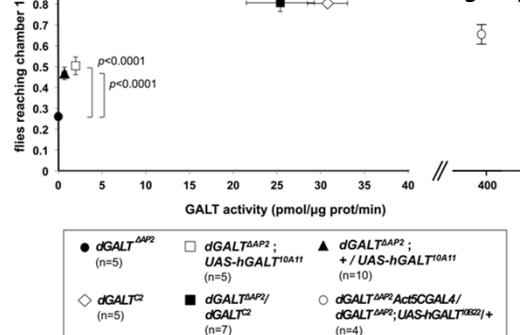
**long-term neuromuscular complication**



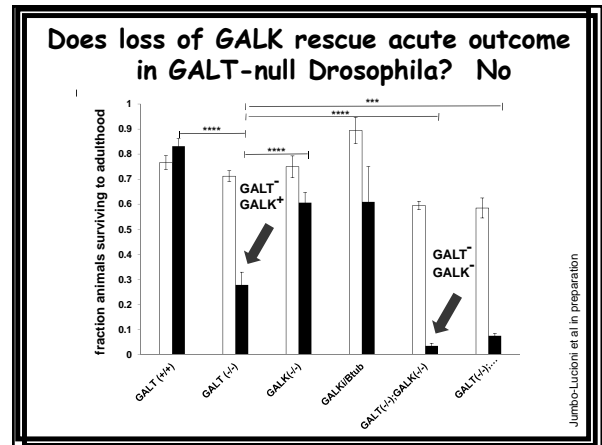
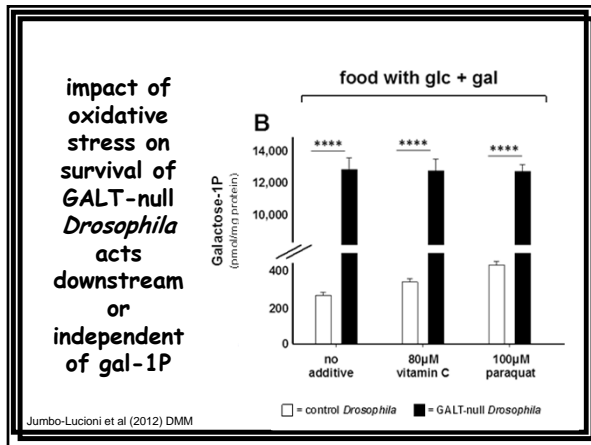
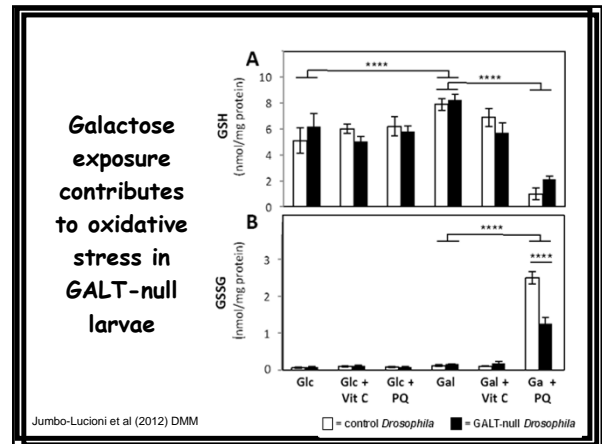
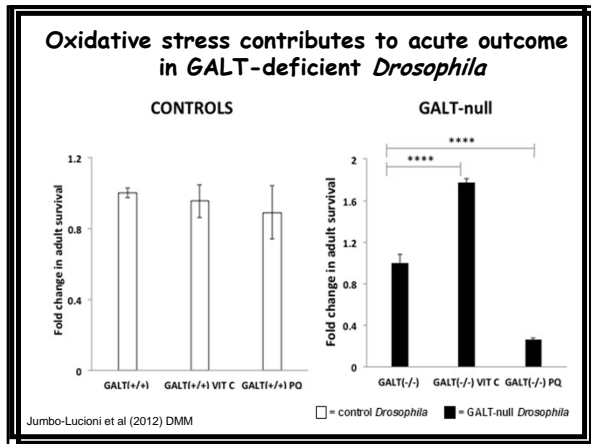
Kushner et al (2010) DMM

**So, now we have an animal model of GALT-deficiency that demonstrates both acute and long-term complications; how can we use it to learn about galactosemia?**

**a little bit of GALT activity goes a long way**



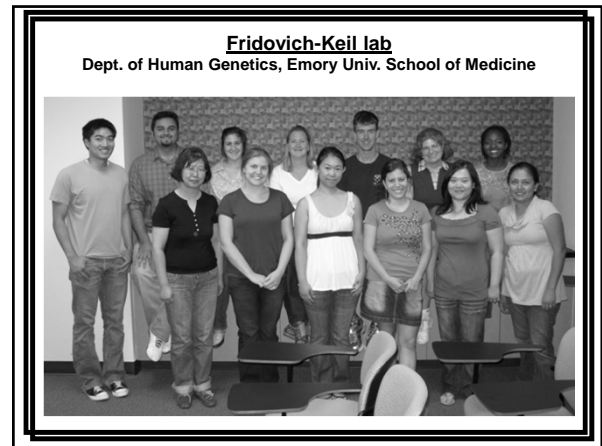
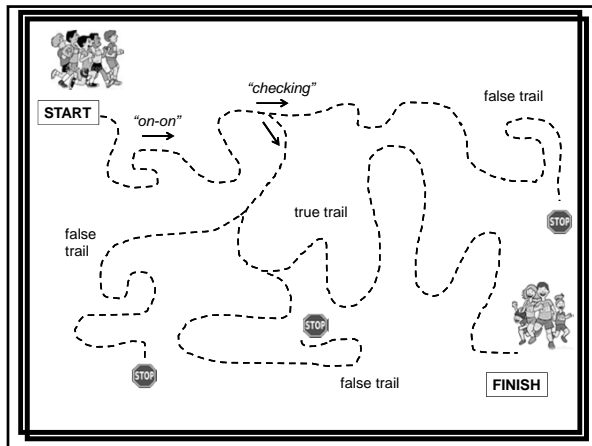
Ryan et al (2012) DMM



## What's next?

### What can YOU do to help?

- Please participate in research!
  - Several teams doing research here at the conference
- Please encourage your representatives in government to support funding for biomedical research (NIH budget).



**Thank you...**