

# EGS/GalNet 2020

## Future treatment strategies

Prof E Rubio Gozalbo

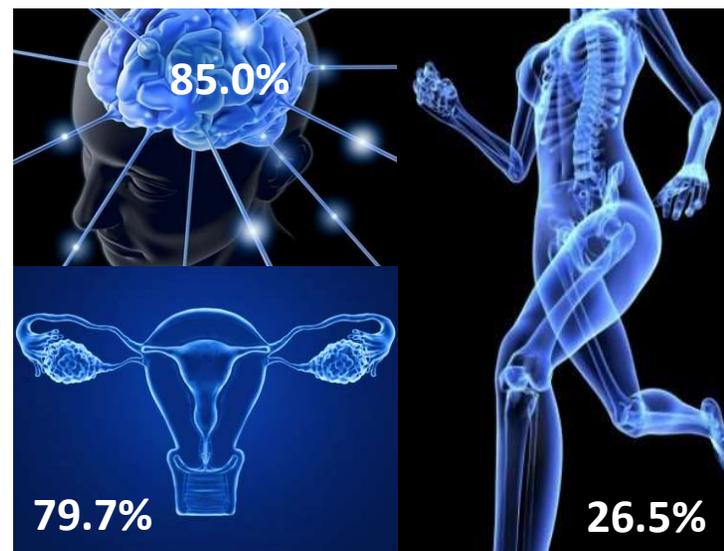
Prof G Berry



# Future treatment strategies for Classic Galactosemia

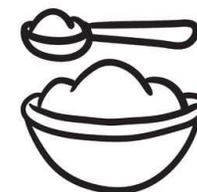
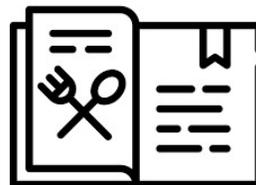
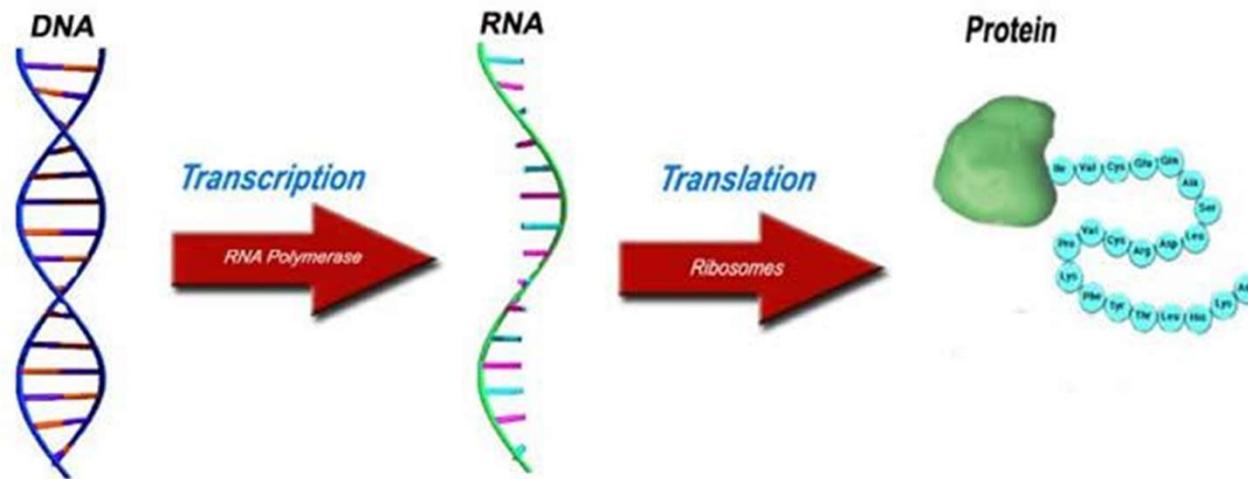
- Overview of different potential strategies
- Clinical/technical challenges discussion

# Complications despite diet

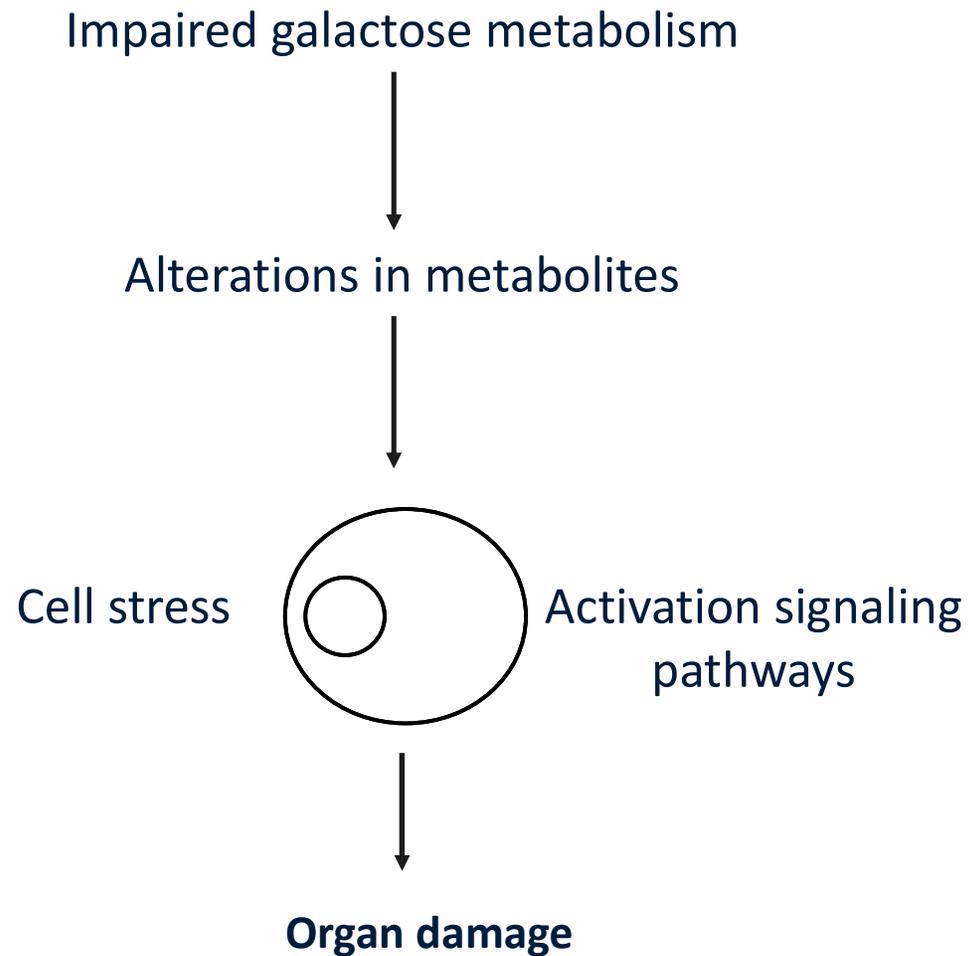


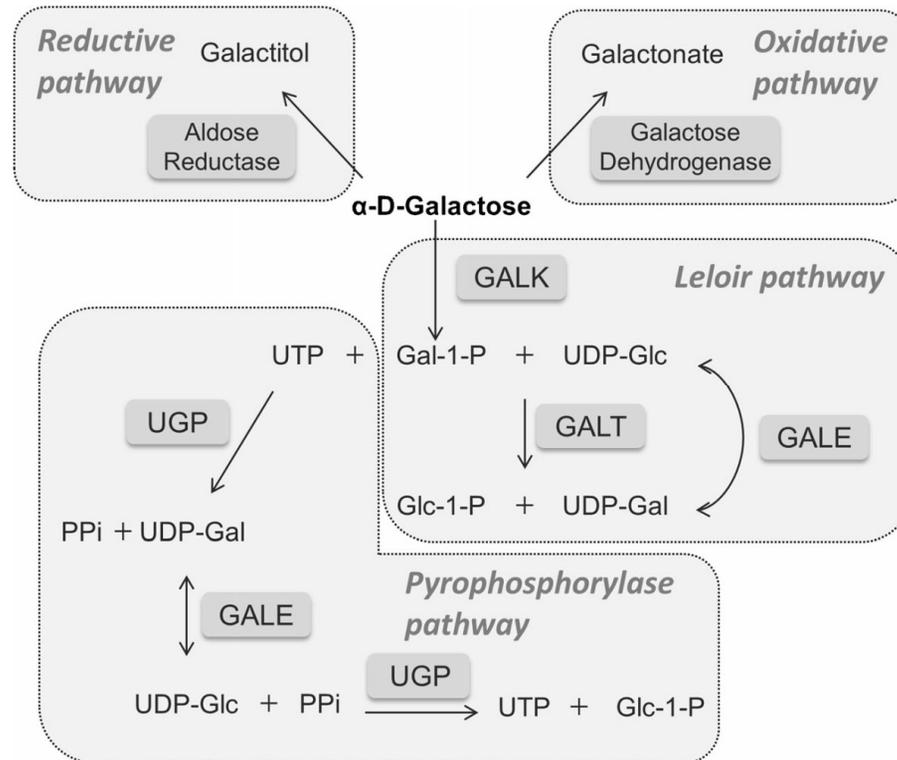
*The natural history of classic galactosemia (2019) OJRD, GalNet*

# Classic galactosemia: hereditary disease

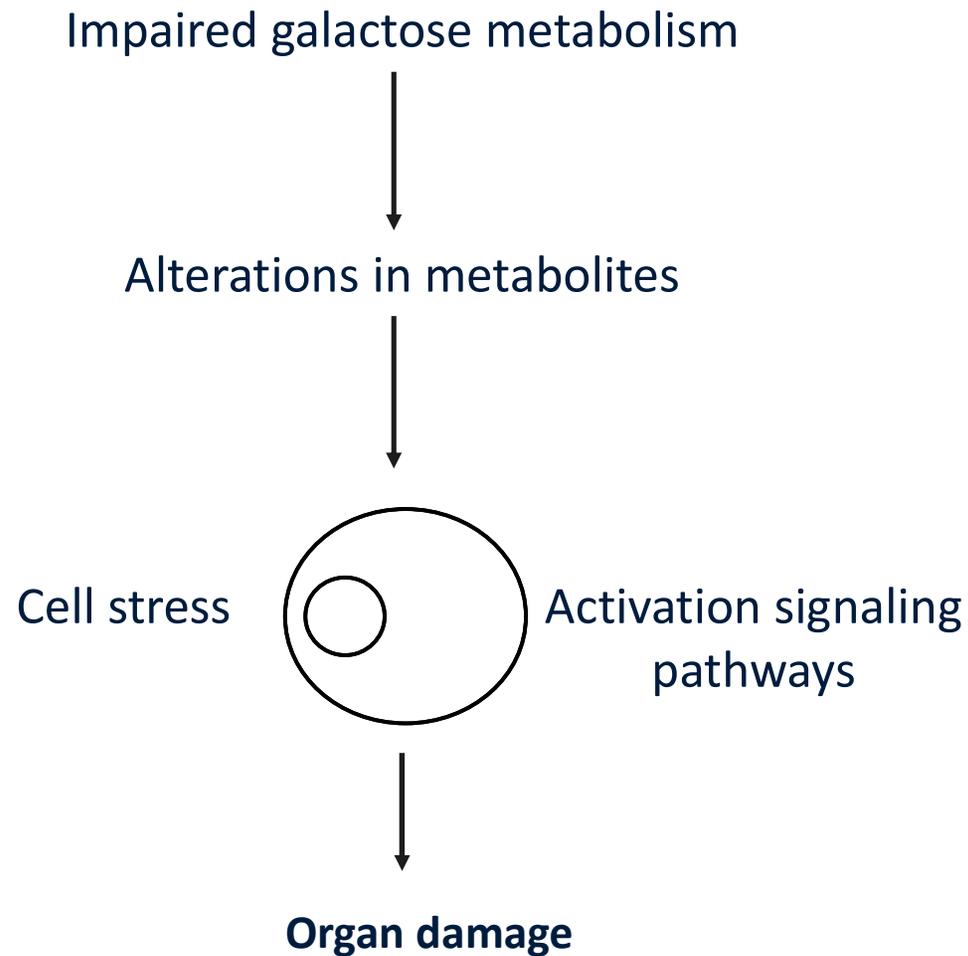


# Genetic defect leads to complex cascade of events





# Genetic defect leads to complex cascade of events



# **New therapies strategies**

**1) rescue GALT activity**

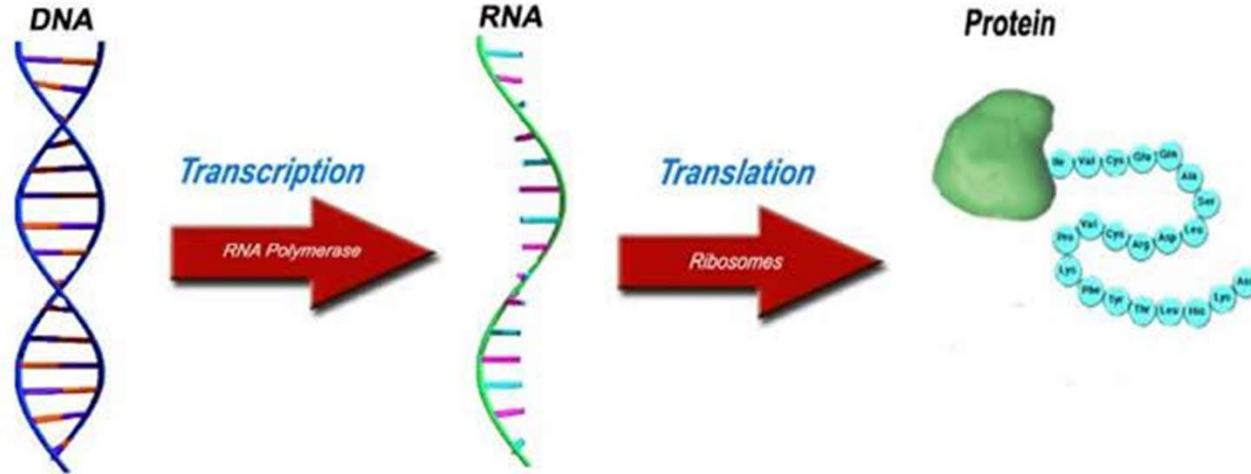
**2) influence cascade of events**

# Strategies to rescue GALT activity

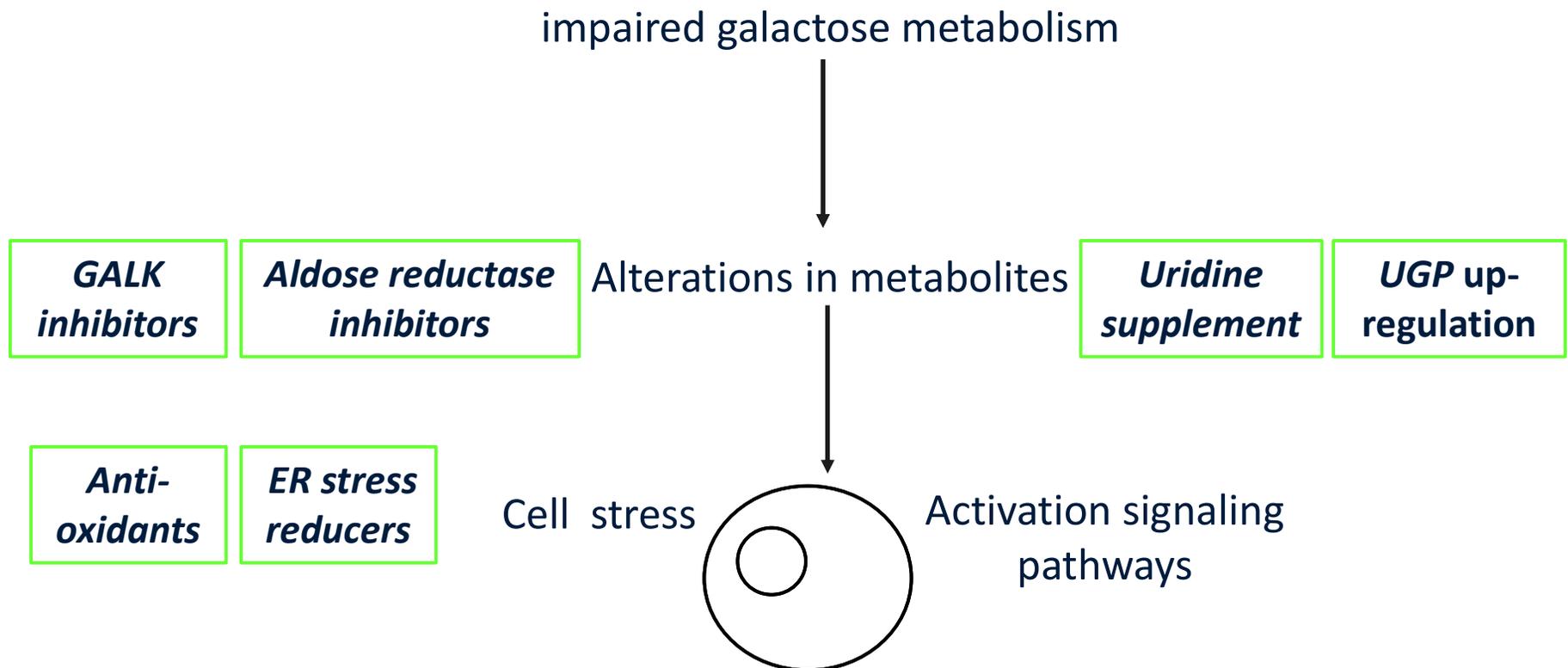
**Gene  
therapy**

**mRNA  
therapy**

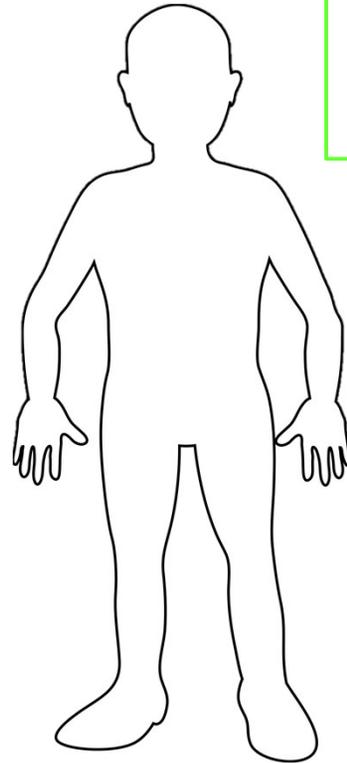
**Chaperones**



# Strategies to influence cascade of events



***Transcranial  
Alternating  
Current  
Stimulation  
(tACS)***



# Rescue GALT activity: Gene therapy



*Fridovich-Keil's group*

- Use of a viral system that 'infects' galactosemia rats with the "normal" GALT gene
- 7 rats, period 14 days
- Rats  $\neq$  humans
- + GALT protein/activity
- + Lowering of metabolites
- + No adverse events



*Kent Lai's group*

- Use of a viral system that 'infects' galactosemia mice with the "normal" GALT gene
- Used two different vectors
- Mice  $\neq$  humans
- + GALT protein/activity
- + Lowering of metabolites (Gal-1P)

# Rescue GALT activity: mRNA therapy



Kent Lai's  
group

- Liver injection at 8 weeks
  - Evaluation after 14 days
  - Mouse  $\neq$  humans
- + Successful delivery and functional GALT
  - + Lowering of metabolites
  - + No adverse effects



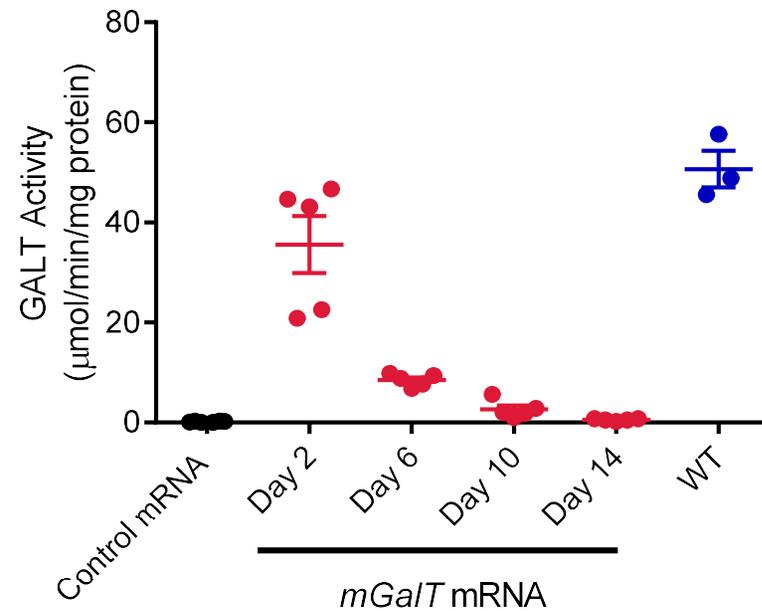
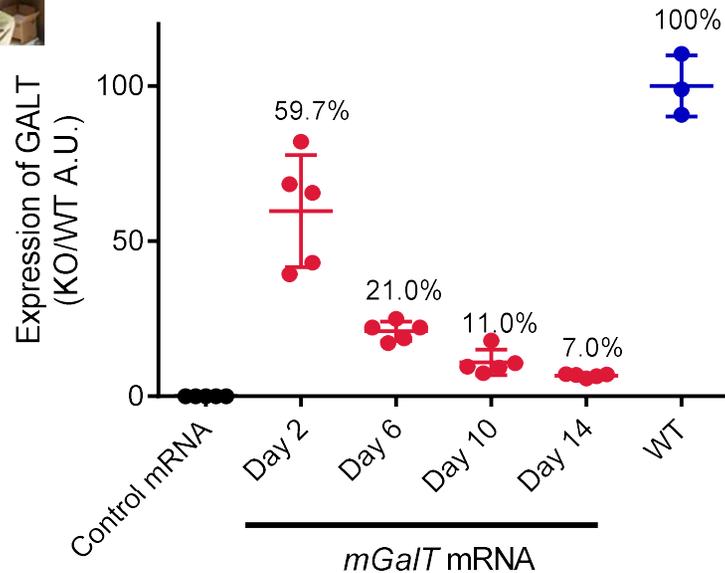
*Estela Rubio-Gozalbo's*  
*group*

- Injection at day 0, one cell stage
  - Evaluation at 5 days old
  - Zebrafish  $\neq$  humans
- + Successful delivery and functional GALT
  - + No adverse effects
  - + Distribution in organs under study

# Rescue GALT activity: mRNA therapy



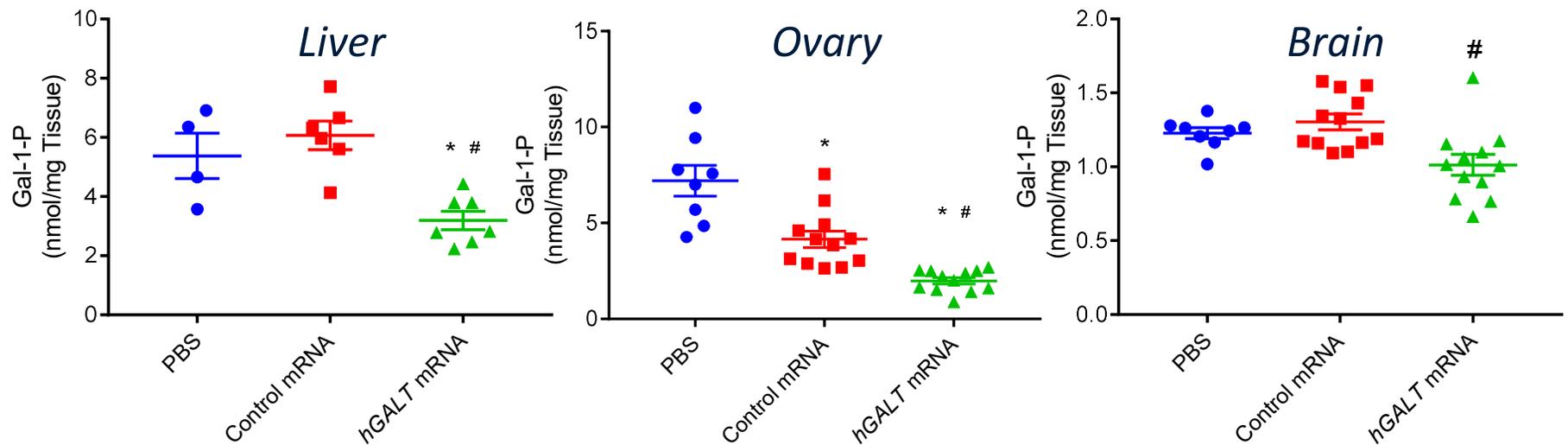
- I.V. injections at 8 weeks
- Half life of ~3 days in the liver bi-weekly and single dosage
- Evaluation after 14 days
- Mouse  $\neq$  humans
- + Successful delivery and functional GALT
- + Lowering metabolites
- + Overcoming neonatal galactose sensitivity



# Rescue GALT activity: mRNA therapy



Bi-weekly dosage GALT mRNA, 4 dosis



# Rescue GALT activity: mRNA therapy



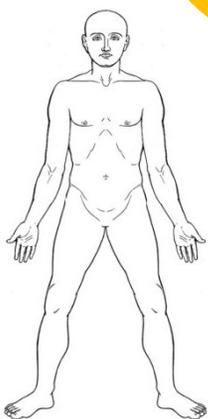
*Estela Rubio-  
Gozalbo's group*

- Injection mRNA at day 0, in the one cell stage
- Evaluation at 5 days old
- Two delivery methods tested
- Zebrafish  $\neq$  humans
- + Successful delivery and functional GALT
- + No adverse effects
- + Distribution in organs under study

# Strategies to influence cascade of events: Aldose Reductase Inhibitors, target galactitol

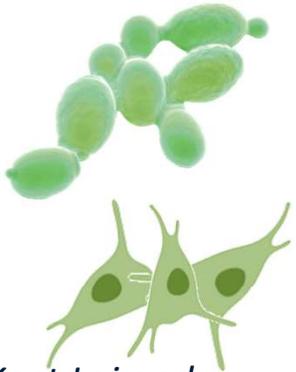


- Homozygous GALT-null rats
- Different inhibitors tested
- + Reduction of galactitol levels in plasma, liver and brain
- + Prevention of cataracts due to lower galactitol
- + Oral administration



Investigate safety and influence on the longer-term effects on the cognitive and neurological symptoms of galactosemia

## GALK inhibitors: target Gal-1-P



*Kent Lai and  
Wyatt Yue's groups*

- + Galactose toxicity was inhibited
- + Lower Gal-1-P
- + Positive effect on cell stress
- Gal-1-P may not be the sole pathogenic agent
- Influence on clinical phenotype to be studied
- Yeast, fibroblasts  $\neq$  humans

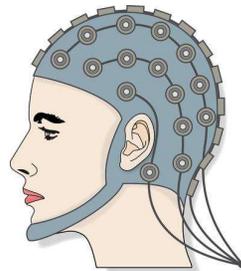


*Fridovich-Keil's  
group*

- + At first movement defects corrected
- + Lower Gal-1-P
- + No adverse effect on survival
- Negative impact on motor skills (climbing) and fertility on the long term
- Fruitfly's  $\neq$  humans

## Strategies to influence cascade of events: (tACS)

Neuronal oscillations/brainwaves related to language and motor tasks are different in classic galactosemia compared to healthy controls



tACS: manipulation of intrinsic cortical oscillations (that are different) with externally applied electrical frequencies

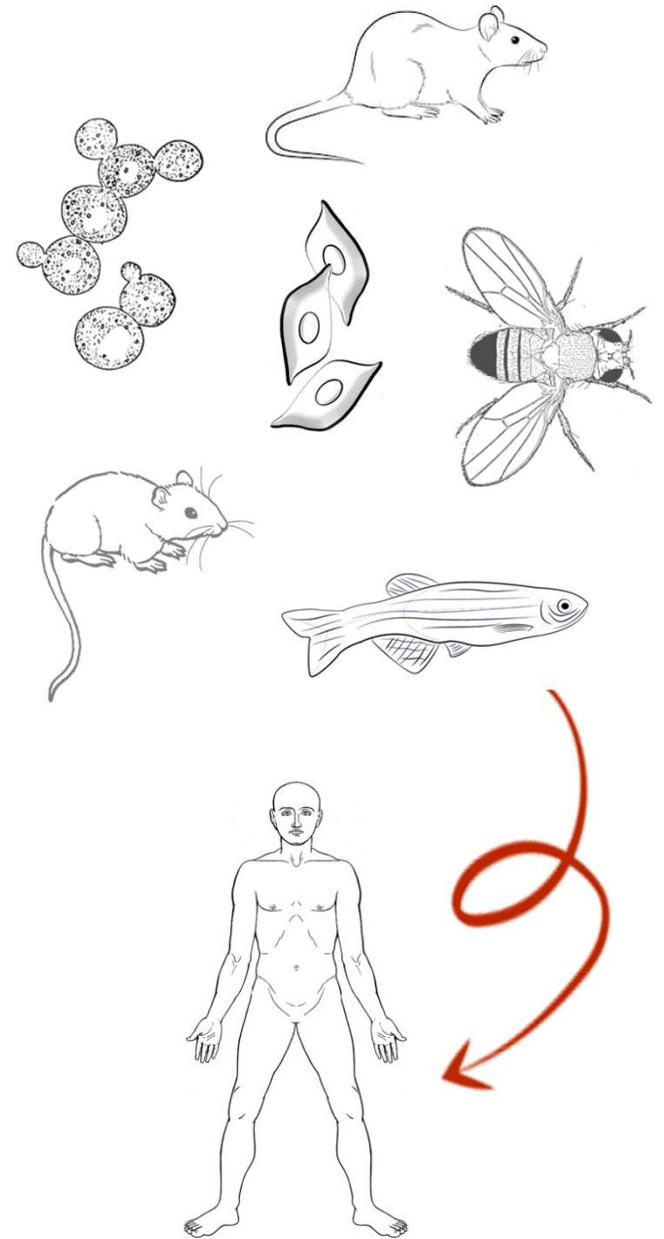
- Improve language/motor behavior
- Compare pre- and post stimulation

# Where do we stand now?

- Rapid development of various treatment strategies
- What are the strengths and limitations of the different modalities?
- And the clinical and technical challenges?
- Different complications might require different treatment
- Combination of treatments?

# Challenges

- Animals  $\neq$  humans
- Safety!
- When and whom to treat?  
Window of opportunity  
for brain?  
for fertility?
- Burden of therapy: daily pills vs. repeated  
injections for mRNA?



## Q&A

- You can ask your questions now via the Q&A button
- Move your mouse to get the Zoom menu bar at the bottom of your screen
- The panelists will try to answer your question or combine with other questions
- If time runs short, we may have to 'dismiss' your question
- If your question wasn't answered, you can send your question to [chairman@galactosaemia.eu](mailto:chairman@galactosaemia.eu)

