RÉUNION DE PRINTEMPS
DE LA SFEIM
SOCIÉTÉ FRANÇAISE
POUR L'ÉTUDE DES ERREURS
INNÉES DU MÉTABOLISME

Cerveau et métabolisme » 18 et 19 JUIN 2018 - Bruxelles, Hôtel Bloom

Classic galactosemia and brain damage

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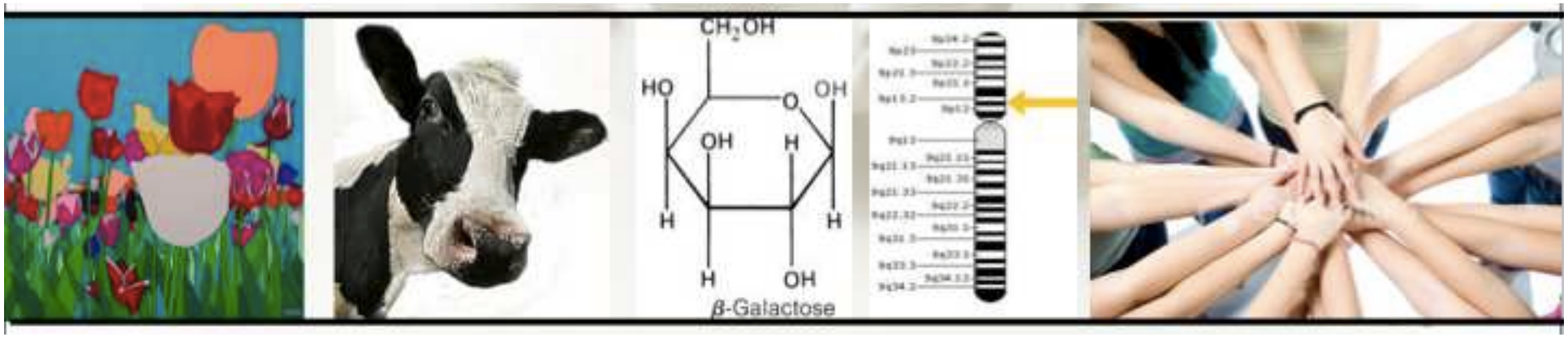
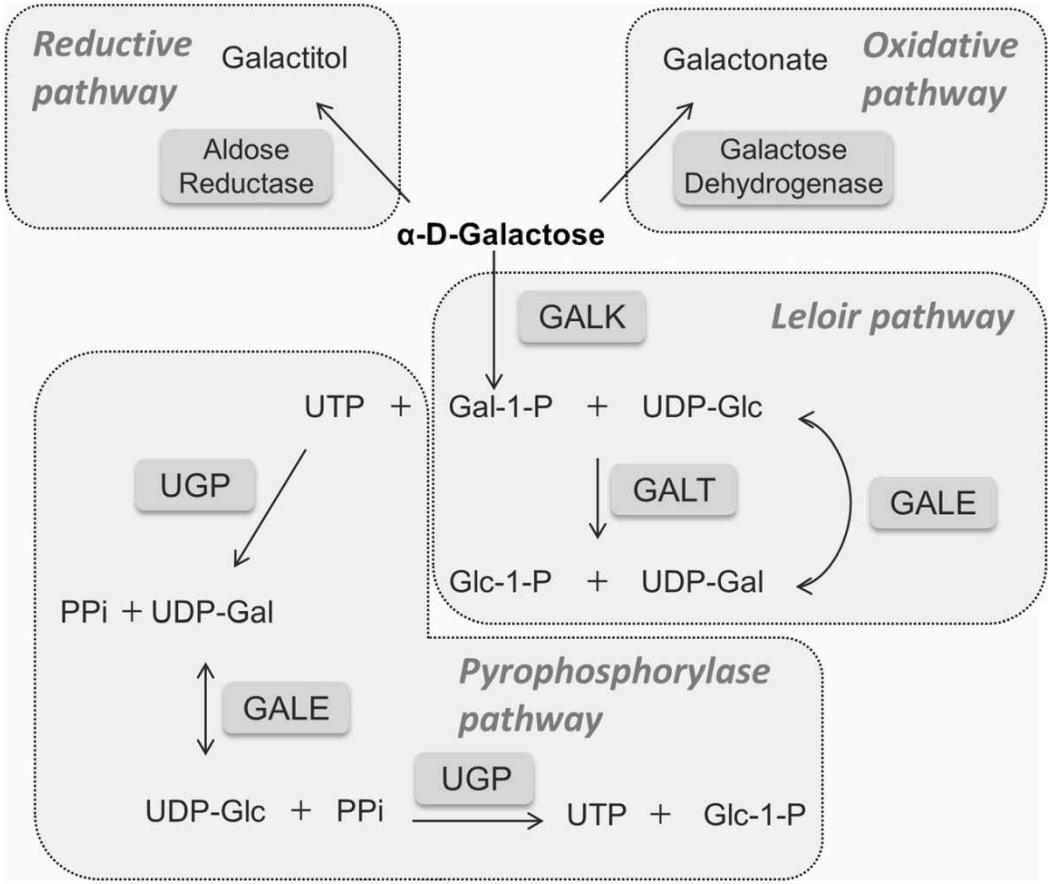
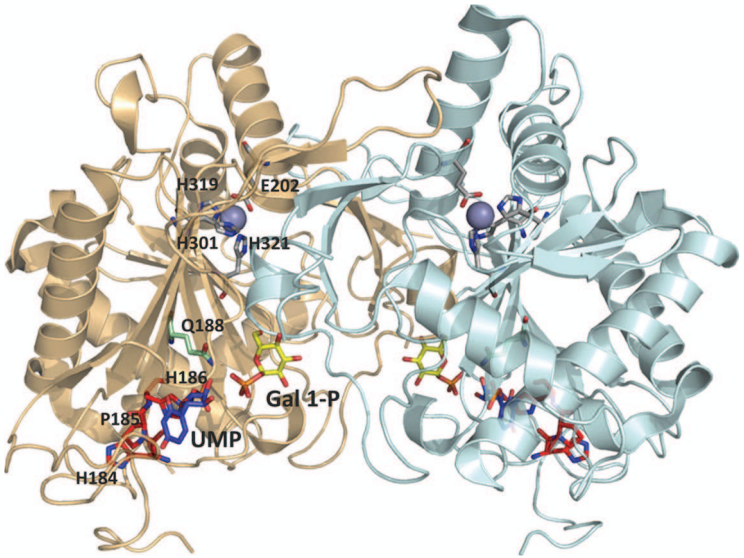
Galactose

- sugar, abundant in dairy milk as lactose (100 ml cow milk = 2400 mg galactose)
- *galakt* = milk in Greek
- lactose = galactose + glucose
- galactose important for energy, glycosylation and other processes
- endogenous synthesis 0,5 - 1mg/kg/hr

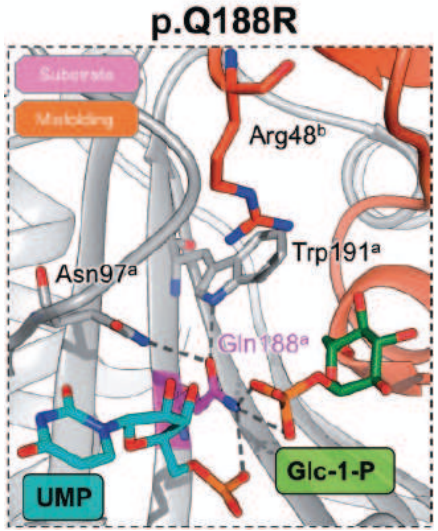


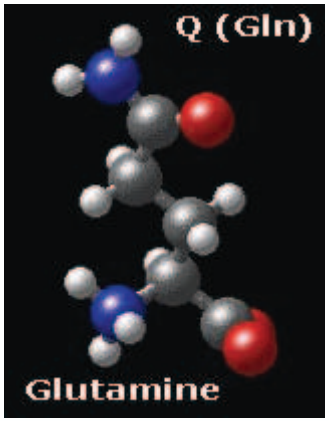
Hereditary galactosemia

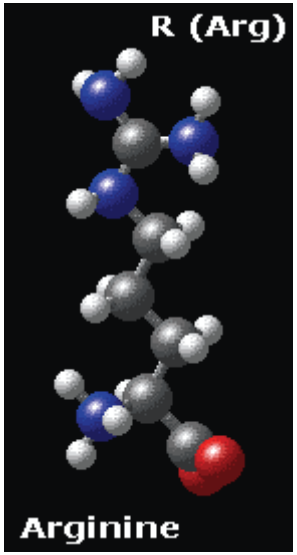


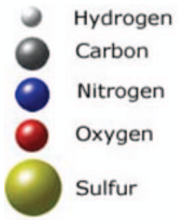


AR, mutations in *GALT* gen (>300)
located 9p13
c. 563A>G (p.Q188R) (ca.80%)
Prevalence 1:50,000 Western world





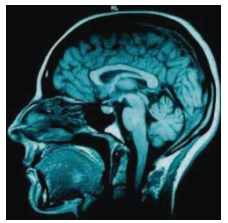


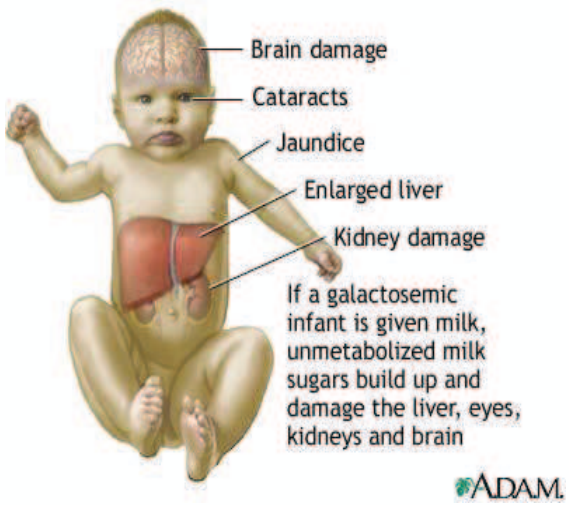


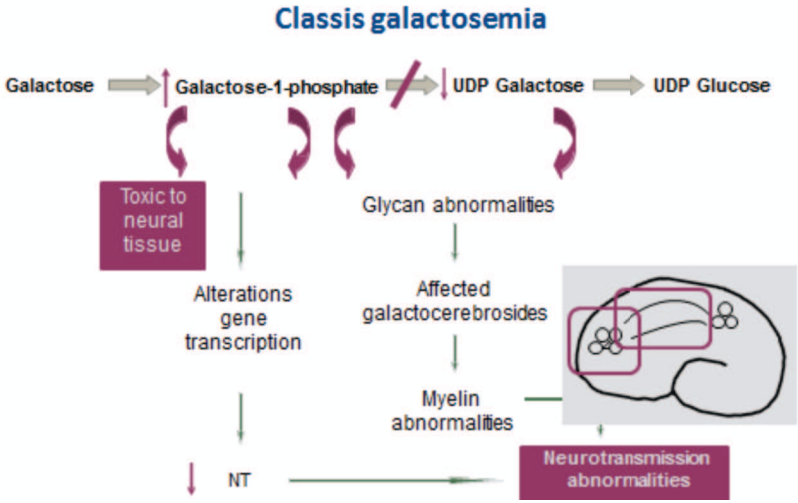
Neonatal screening

Diet reverses neonatal picture but does not prevent complications

Endogenous production!







Lower Intelligence (45-72%)

Executive functions

Language and speech problems (38-88%)

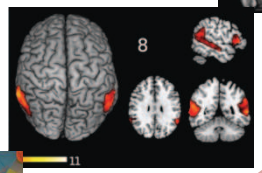
Learning difficulties

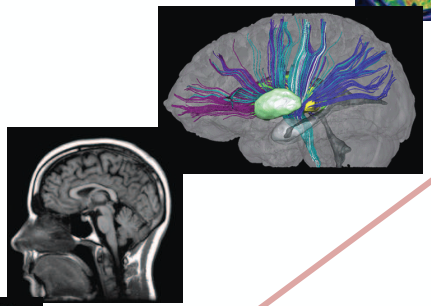
Slower Information processing

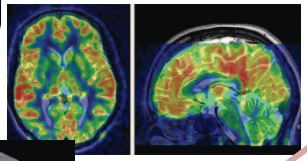
Social engagement disabilities

Motor disturbances

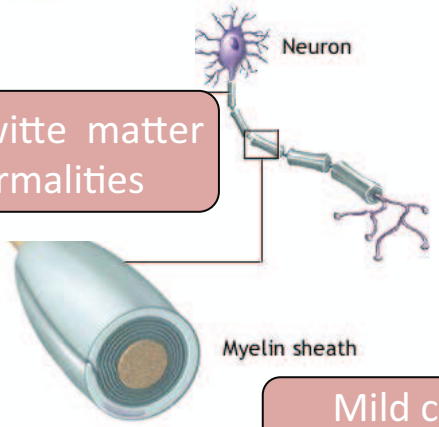
Tremor, dystonia, ataxia, dysmethria, dysarthria







Diffuse witte matter abnormalities



Mild cortical atrophy

Is cognitive impairment progressive?

- Some cross-sectional studies report a negative correlation between age and performance
- Longitudinal studies do not
- In a cross-sectional study in which we participated, IQ did not decline in subjects between 18 and 59 years of age

Psychiatry

- Psychiatric symptoms and emotional problems often reported
- Most frequent: depression, anxiety, obsessive compulsive disorder and autism spectrum disorder
- **Need for periodic evaluation and early intervention**

Study of the brain on line

- During an active language production task and in rest

  - **fMRI to locate networks and functional connectivity (which regions work together during language production and what are the differences between CG patients and controls?**

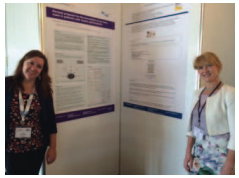
  - **DW-MRI to assess properties in WM microstructure**

- Aim: link brain function to observed language impairments

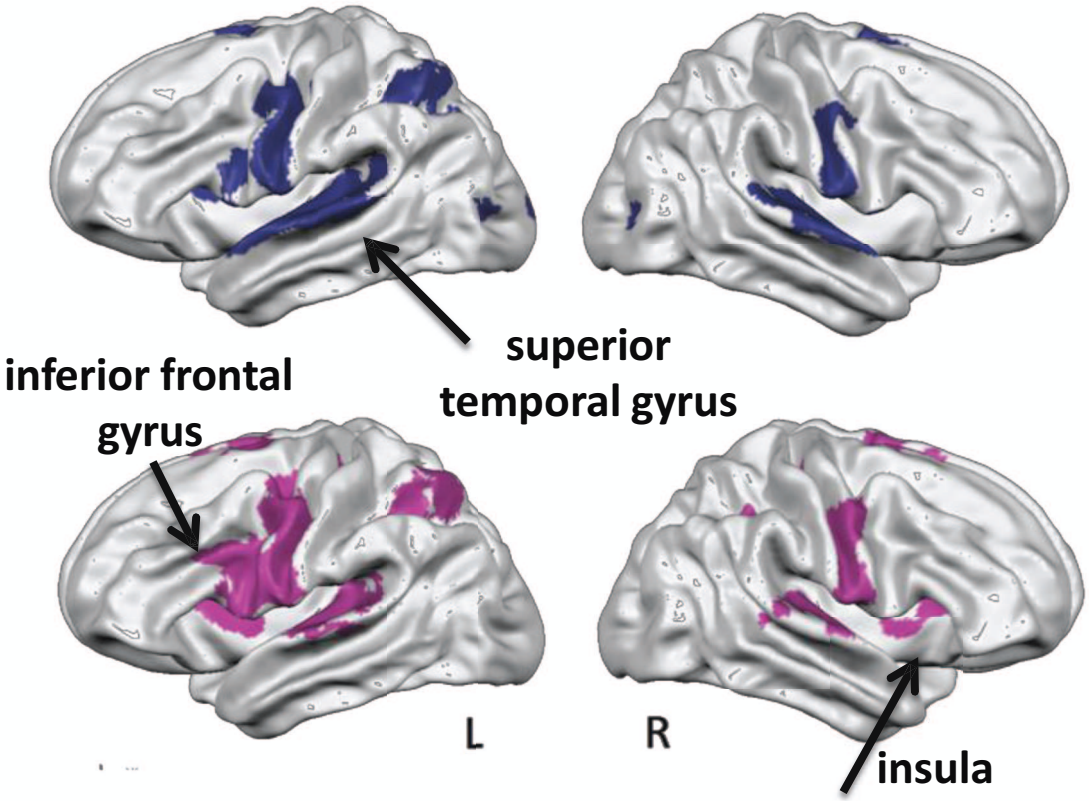
What do we see?

altered neural activity and connectivity in specific brain regions important for language planning and production.

- Patients recruit
  - more left interior frontal areas



  - less left superior temporal regions
  - right insula (whereas controls do not)



Timmers et al. Brain Research 2015

fMRI to evaluate spontaneous functional connectivity during rest

Alterations in several networks:

- **medial prefrontal cortex, parietal lobule and (pre)cuneus, involved in spatial orientation and attention.**
- **insula and superior frontal gyrus -important for sensory-motor integration and motor (speech) planning**
- **occipital regions, linked to visuospatial capacities and working memory**

Van Erven et al. Sci Rep 2017

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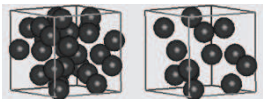
Diffusion MRI in classic galactosemia: NODDI (neurite orientation dispersion and density imaging)

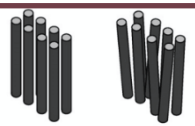
What happens to the white matter microstructure?

Indices of WM microstructure:

density of neurites



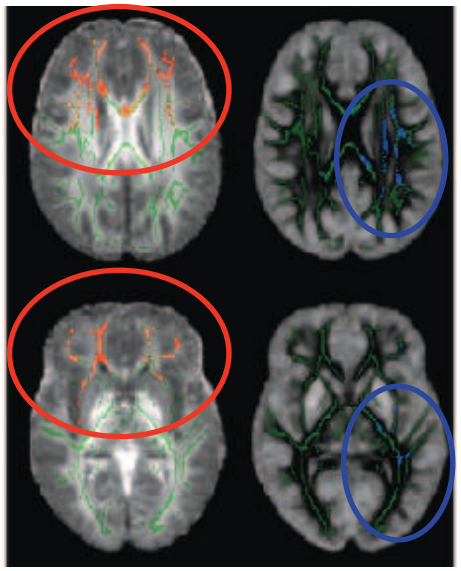
dispersion in orientation



Results:

neurite density:
patients < controls
bilateral, anterior regions
> fits with general higher order cognitive impairments

orientation dispersion:
patients > controls
left-lateralized more posterior
> fits with profile of motor / language production abnormalities



Timmers et al. JIMD 2015

What happens to the grey matter?

- A voxel-based morphometry study.

Decreased GM density: bilateral putamen and occipital cortex.

- **Putamen: motor function and control, connected to pre-motor areas and motor cortex; also link to executive functioning, working memory, sequence learning**
- **Bilateral occipital cortex: visuo-spatial involvement**

Increased GM density: bilateral inferior frontal and medial prefrontal cortex

- **IFG: language production**

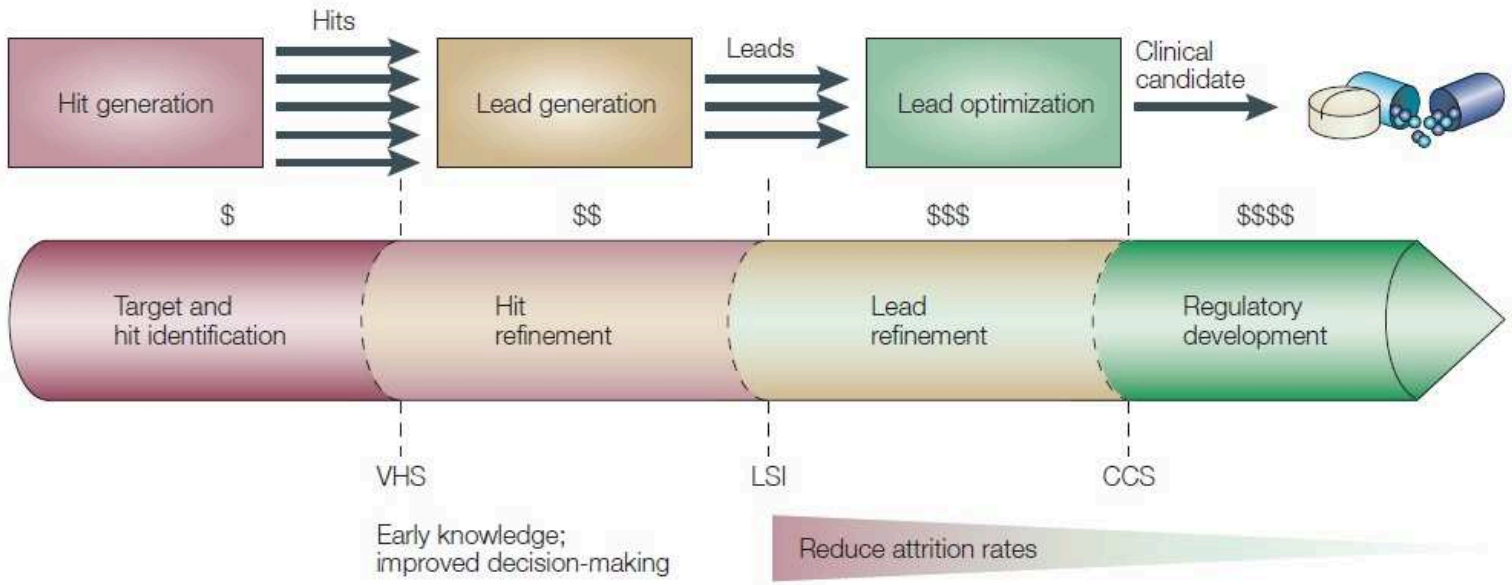
Grey matter density **decreases as well as increases**

Timmers et al. Brain Research 2016

Brain damage despite life long restricted diet

NEED FOR NEW THERAPEUTIC STRATEGIES

Development of novel small molecule therapeutics



HIGH THROUGHPUT SCREENING: Screening (of a compound collection) to identify **hits** in an *in vitro* assay

LEAD: Prototypical chemical structure(s) that demonstrate activity and selectivity in a pharmacological or biochemically relevant screen. Basis for lead optimization and development to identify a clinical candidate.

(*Nature Rev 2003)*

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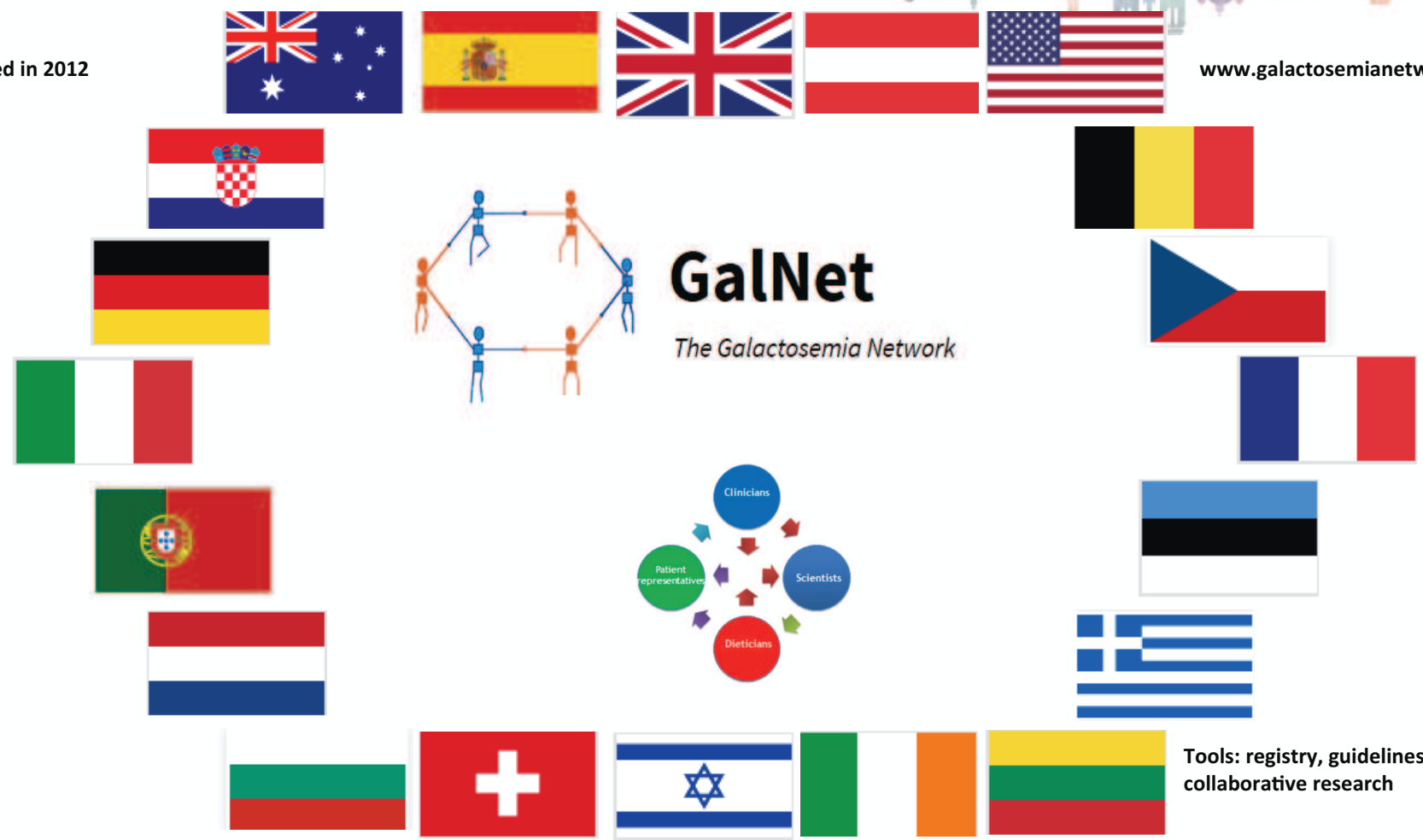
Founded in 2012

www.galactosemianetwork.org



Tools: registry, guidelines and collaborative research

Aim: better outcome of patients

Galactosemias Network (GalNet)
(www.galactosemianetwork.org)

Large screen using biochemical or cell-based assays

Need of large-scale screens using whole organism

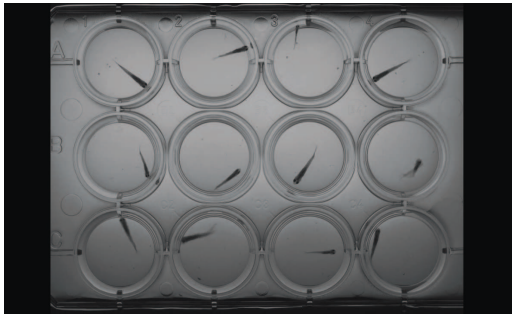
Role for
Zebrafish
(*Danio rerio*)

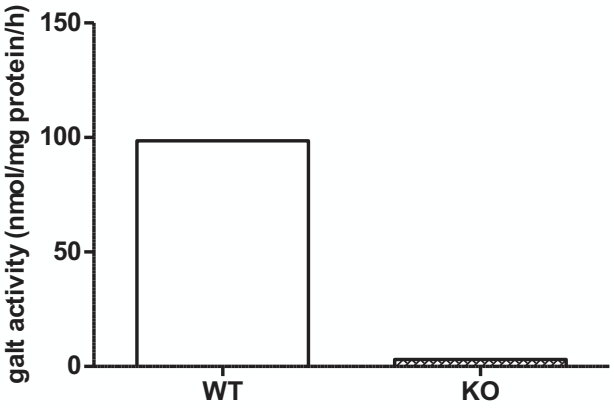
Zebrafish model Classic Galactosemia

Motor activity studies

ZebraBox ®

Exposure to **light** for a period of **60 minutes**



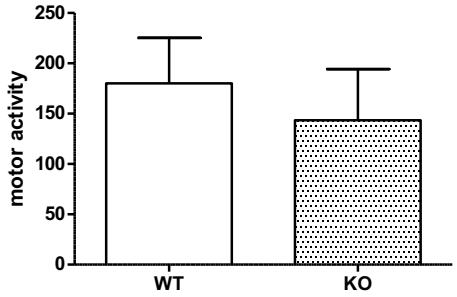


Impaired fertility and motor function in a zebrafish model for classic galactosemia

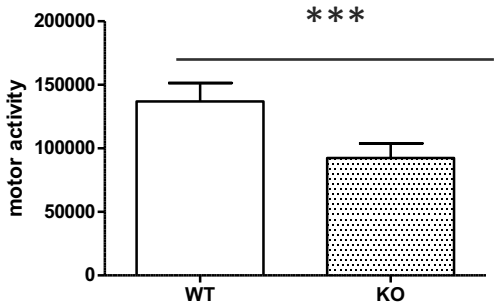
Jo M. Vanoevelen[1,2] · Britt van Erven[1,2,3] · Jörgen Bierau[1] · Xiaoping Huang[4] · Gerard T. Berry[4] · Rein Vos[5] · Ana I. Coelho[1,2,3] · M. Estela Rubio-Gozalbo[1,2,3]

Brain studies: Motor activity

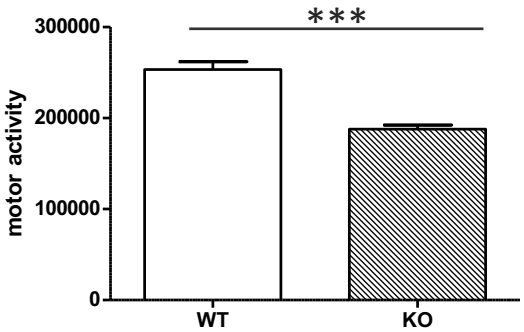
larvae (**5 dpf**)



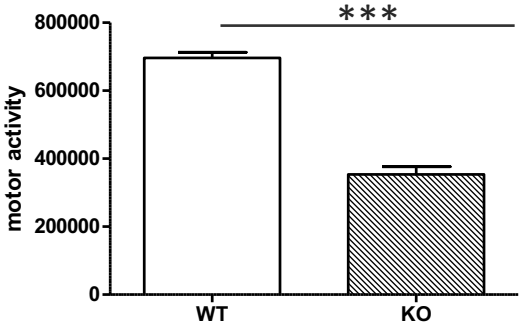
juvenile fish (**4 wpf**)



adult fish (**3 mpf**)



adult fish (**9 mpf**)

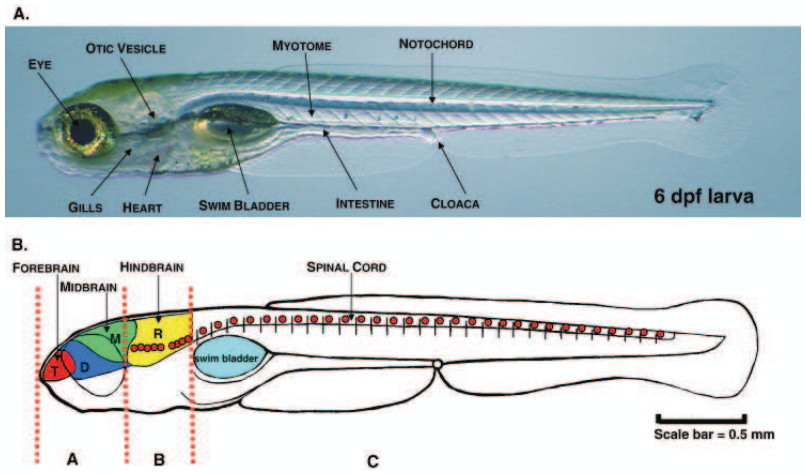


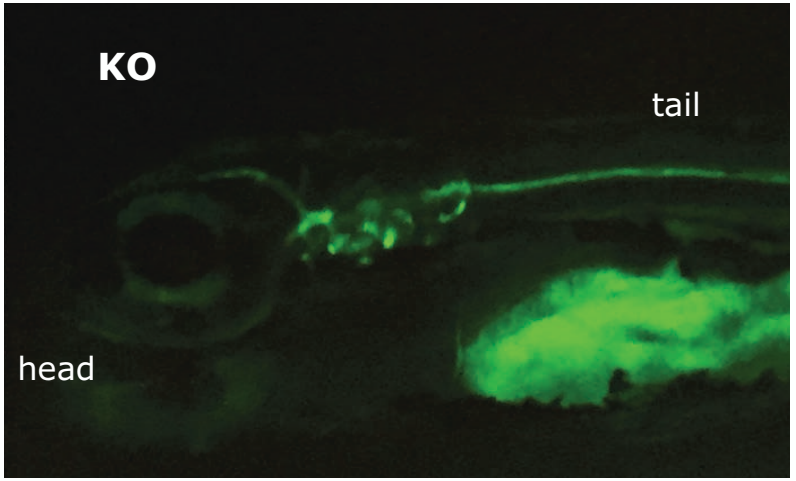
Myelin studies

galt

mbp:GFP reporter line
fluorescent myelin

Larvae at 5 dpf

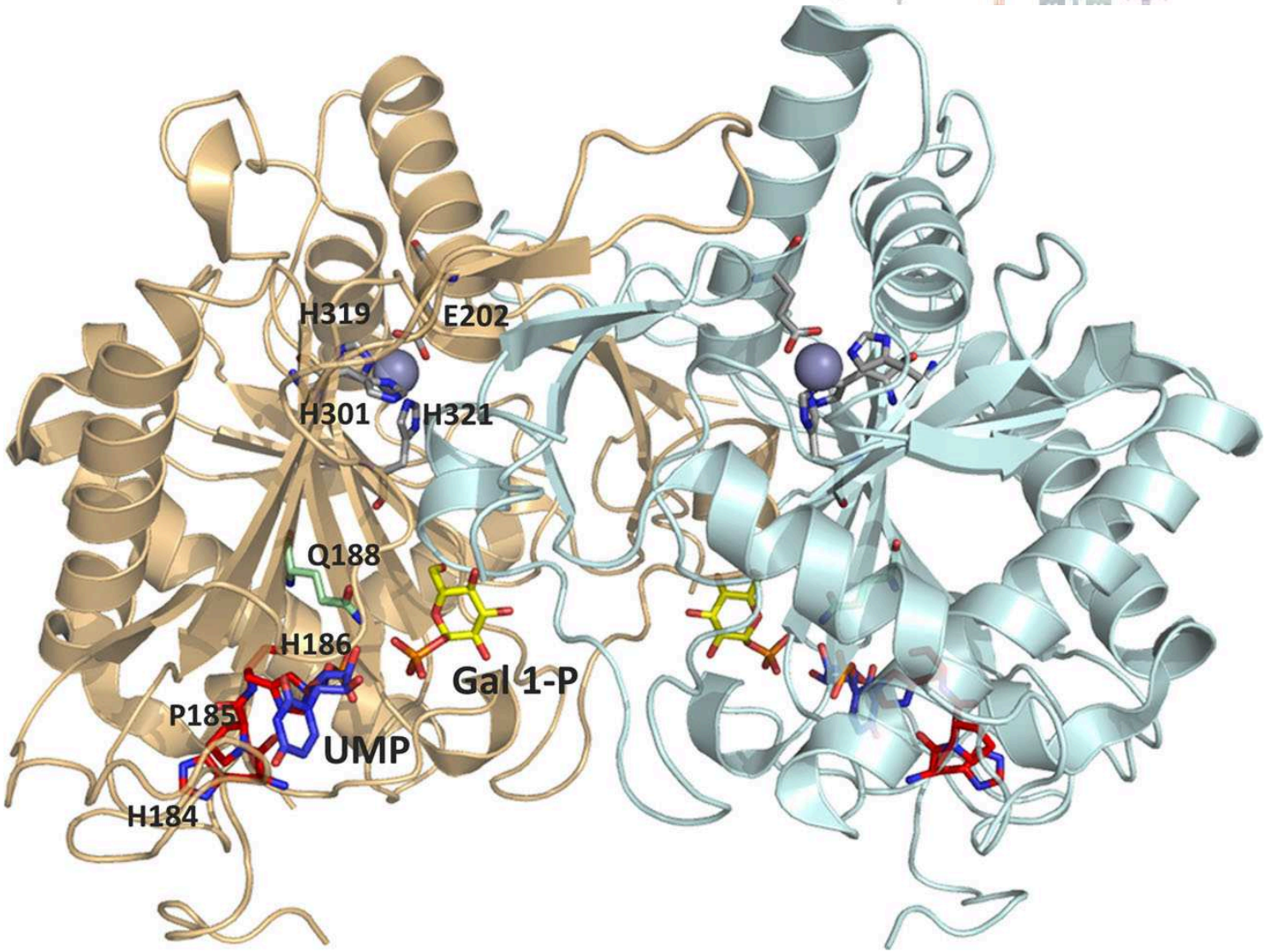




Conclusions

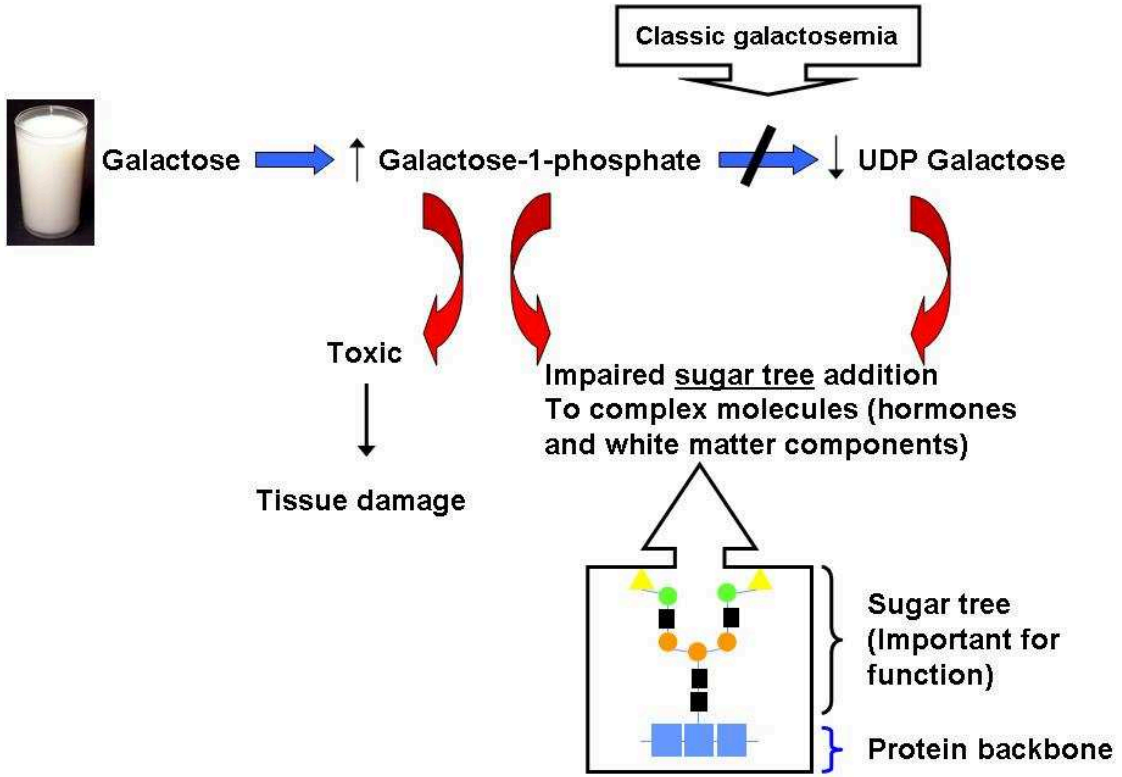
- **Cognitive, neurological and psychiatric complications** despite diet
- Pathophysiology: different mechanisms acting in unison, **not only toxic**
- **Altered** neuronal networks
- **Abnormal white matter** with increased neurite dispersion and lower neurite density
- **Abnormal grey matter** with decrease but also increase in some areas
- Need for periodic **evaluation** and early **intervention**
- Need for **new therapies**

Thank you


H319
E202
H301
H321
Q188
H186
Gal 1-P
P185
UMP
H184

Therapie strategie

Verhogen van GALT enzym activiteit



References

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- White matter microstructure pathology in classic galactosemia revealed by neurite orientation dispersion and density imaging. Timmers I, Zhang H, Bastiani M, Jansma BM, Roebroeck A, **Rubio-Gozalbo ME**. J Inherit Metab Dis. 2015 Mar;38(2):295-304.

- Affected functional networks associated with sentence production in classic galactosemia. Timmers I, van den Hurk J, Hofman PA, Zimmermann LJ, Uludağ K, Jansma BM, **Rubio-Gozalbo ME**. Brain Res. 2015 Aug 7;1616:166-76.

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- Exploration of the Brain in Rest: Resting-State Functional MRI Abnormalities in Patients with Classic Galactosemia. van Erven B, Jansma BM, **Rubio-Gozalbo ME**, Timmers I. Sci Rep. 2017 Aug 22;7(1):9095. doi: 10.1038/s41598-017-09242-w.

- MRS brain : myo-inositol content?

Done in neonates