Galactosemia Foundation 2012 Conference
Research Briefing
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Computational Biology Strategy for the Development of Ligands of GALK Enzyme as Potential Drugs for People with Classic Galactosemia.

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Background

Our activity on galactosemia started in 2004 at the Institute of Food Science, CNR, Italy

Background

We were interested in studying molecular systems (and in particular, proteins) involved in food processes and diseases linked to food by applying bioinformatics approaches such as:

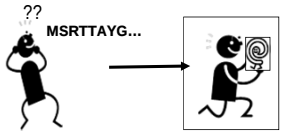
- **molecular analysis**
- **molecular modeling**
- **docking**
- **molecular dynamics simulations**

All of these approaches require **ONLY** a computer to be done!

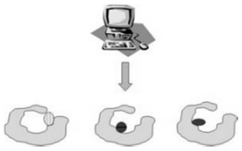
(...well, also some **brain**...☺)

Molecular analysis

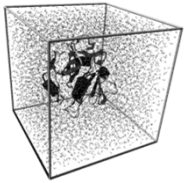
Molecular modeling



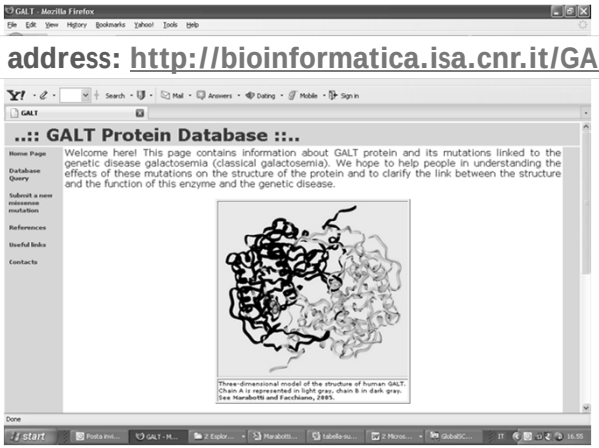
Docking



MD simulations



Background



Web address: http://bioinformatica.isa.cnr.it/GALT/

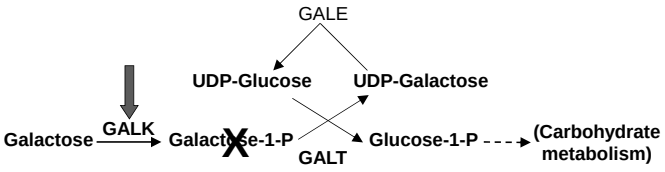
The current project

Computational biology strategy for the development of ligands of GALK enzyme as potential drugs for people with classic galactosemia.

Institute of Biomedical Technologies, CNR, Italy

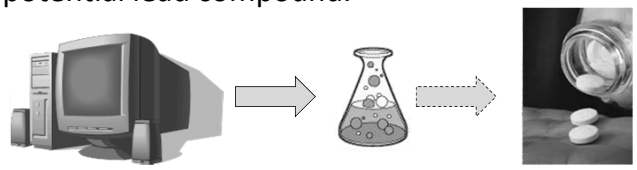
Aims

- To find **ligands able to block GALK enzyme** and to **stop production of galactose-1-P** which is not further metabolized by altered GALT enzyme and which is considered as the main responsible for symptoms in galactosemic patients (Wierenga et al, 2008):

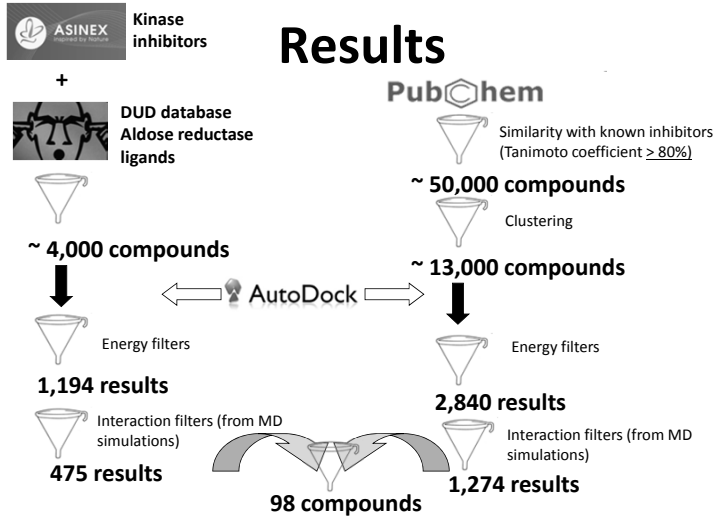


Methods

- A **virtual screening pipeline** combined with a **molecular dynamics simulation protocol** to find the best ligands to be experimentally tested for further characterization.
- This will reduce **costs and time** for finding a potential lead compound.



Results



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Ongoing activities

98 ligands selected (including 33 with the highest selectivity towards GALK enzyme) **are currently being experimentally tested.**

The results of these tests will give us information about:

- the **correctness** of our approach
- the **physico-chemical features** of the most promising compounds tested
- their **potential to become lead compounds** for a future development as drugs.

Conclusions

☺ Our simulation studies were able to **dissect the interaction between GALK enzyme and its ligands** at molecular level

☺ This new knowledge **increases the chance of finding more promising GALK inhibitors** with a focused virtual screening approach

☺ Moreover, this promotes the **design of new families of compounds** targeting GALK with higher affinity, reducing the risk of side effects and optimizing their chemical features.

Acknowledgments

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- Kent Lai (Dept. Pediatrics, University of Utah, USA)
- ...and all of you for your kind attention!!!