



# Bioinformatics Analysis for Understanding the Biology of Ageing

Chemical and Biological Systems Engineering Laboratory

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#### Ageing is an extremely complex process

 Marked by progressive functional and physiological decline and culminating in death.

 Ageing is a major risk factor of a plethora of human diseases including cancer, cardiovascular and neurodegenerative diseases. However the role of ageing in causing or increasing vulnerability is unknown.



The Hallmarks of Aging, Cell, 153, 2013

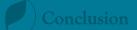












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#### Ageing and metabolism are closely connected

- Dietary or calorie restriction is the most successful ageing intervention strategy in laboratory across different organisms.
- However, the biology and mechanism of ageing is poorly understood and so are the specific metabolic pathways involved in the ageing process.



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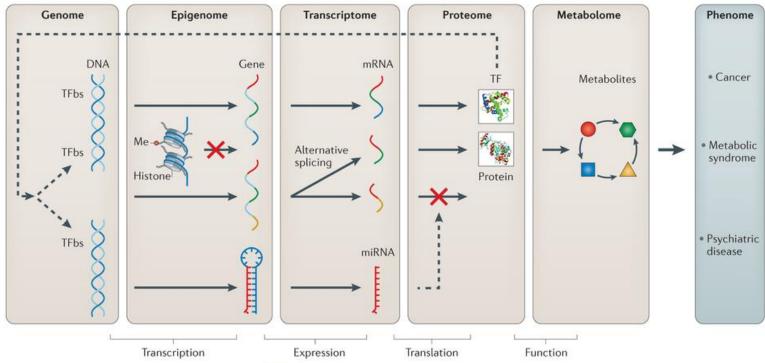






#### Post-Genomic era explosion of data

- Complexity of the ageing process motivated a system oriented approach.
- Comprehensive knowledge on metabolic networks in humans and other model organisms.
- Availability of high-throughput omics data with increasing ease and decreasing cost shifts the focus of understanding and making sense of the immense data.











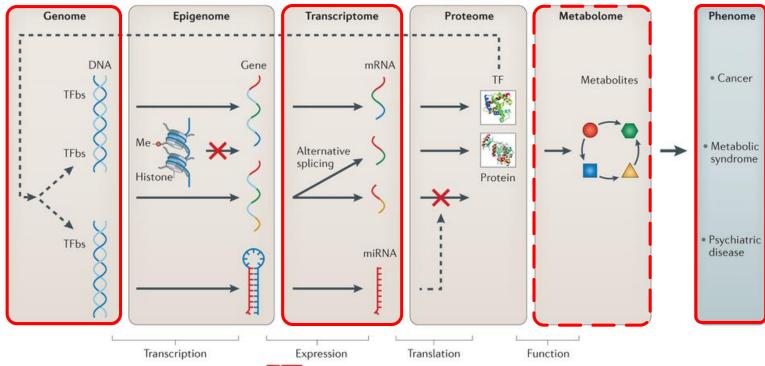






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### **Objectives**



- Shedding light on specific molecular pathways and biological processes that modulate ageing and the onset and progression of multiple age-related diseases.
- Validating central regulators of the ageing process using a lifespan study in a model organism.
- How does metabolism affects ageing and vice versa
  - Translating human metabolic alterations and perturbations such as dietary restrictions during ageing and translate these changes to phenotypes.
  - Mechanistic explanations underlying different metabolic diseases.







### **Objectives**

- How does ageing causes or increases the vulnerability to several "age-related" diseases
  - Shedding light on specific molecular pathways and biological processes that modulate ageing and the onset and progression of multiple age-related diseases.
  - Validating central regulators of the ageing process using a lifespan study in a model organism.
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Mechanistic explanations underlying different metabolic diseases.

#### Age-related diseases

- Neurodegenrative
- Cardiovascular

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- Metabolic disorder
- Cancer
- Diabetes







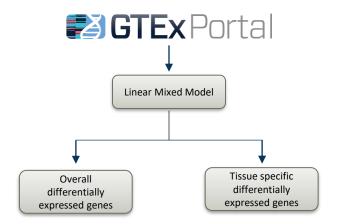














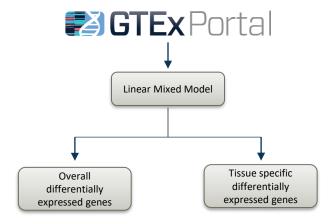


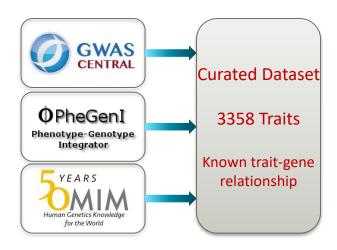














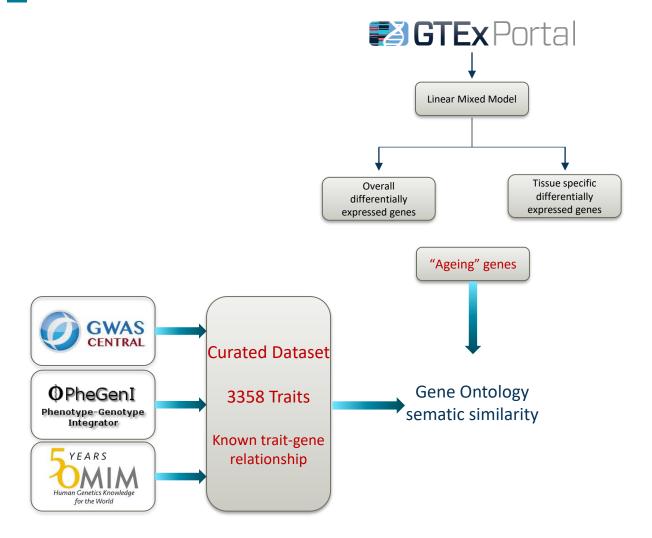














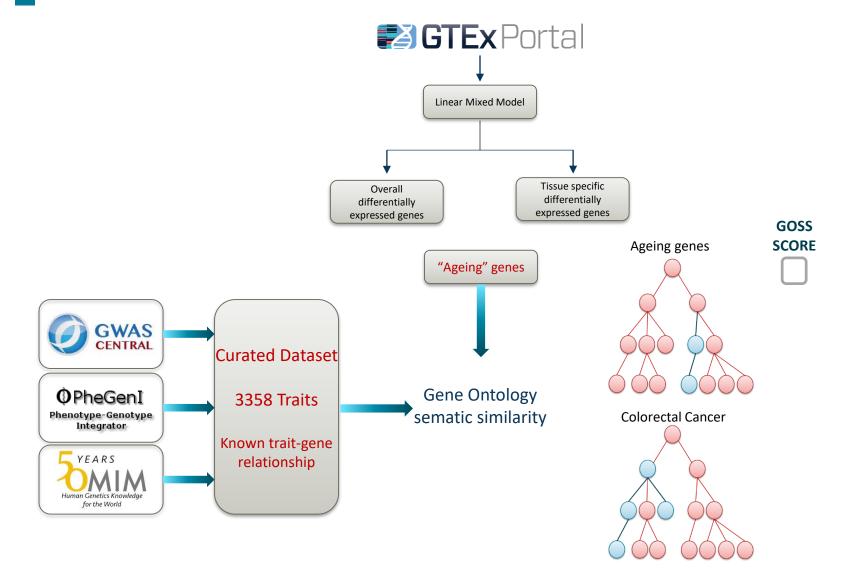
















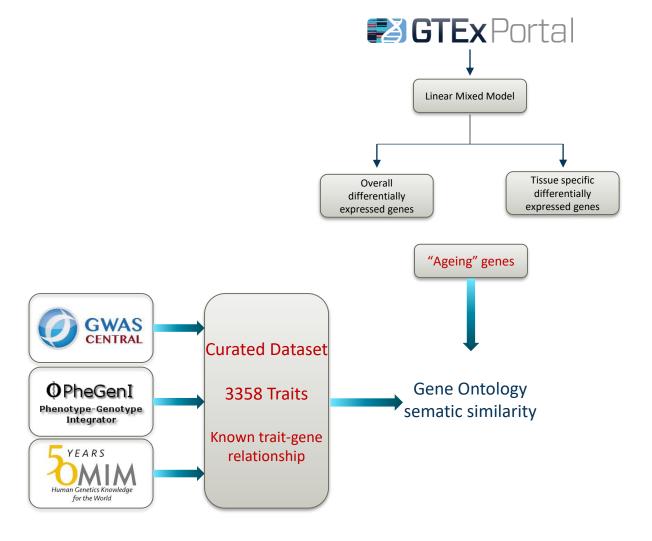












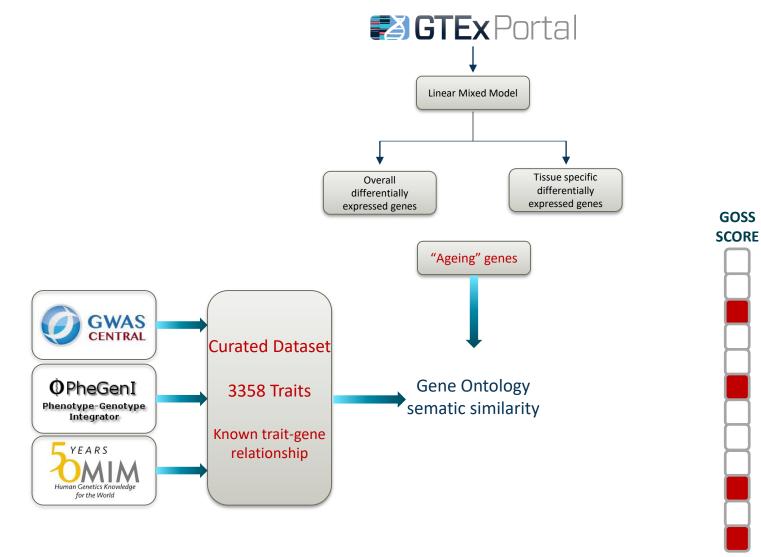








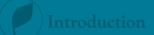








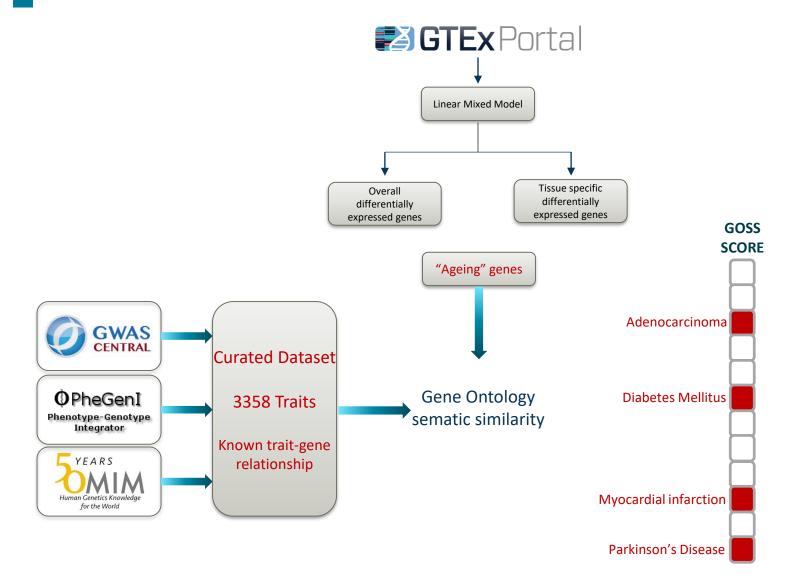








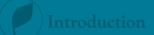








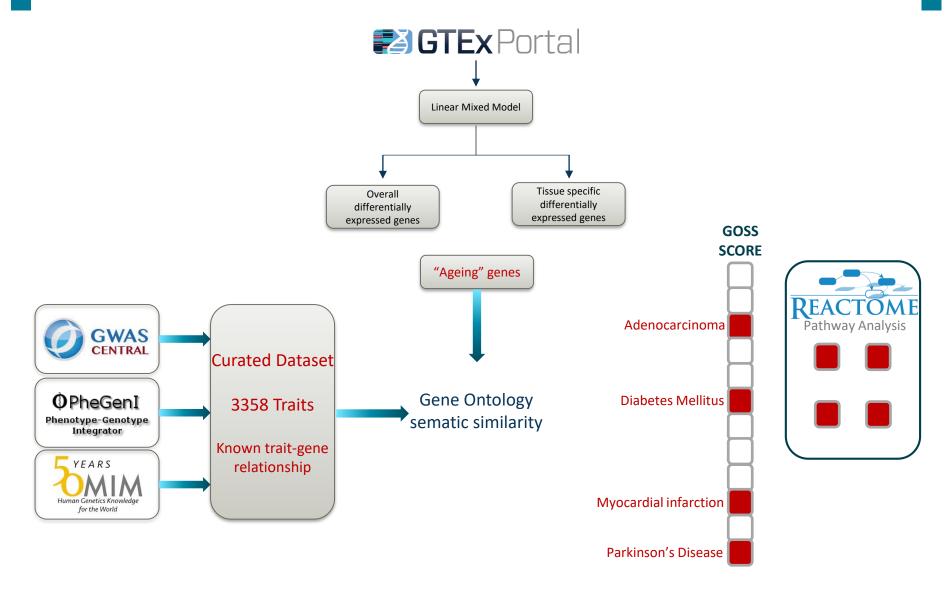
























#### Human Traits similar to Ageing – Overall DE

#### **Human Traits**

Adenocarcinoma of lung

Basal cell carcinoma

Colorectal cancer

Diabetes mellitus

Glioma

Hepatocellular cancer

Kaposi sarcoma

Lymphoma

Myocardial infarction

Ovarian cancer

Squamous cell carcinoma

T-cell prolymphocytic leukemia

Thyroid carcinoma

Acampomelic campomelic dysplasia

Aplastic anemia

**Budd-Chiari syndrome** 

Cardiovascular function

Crohn disease-associated growth failure

Martsolf syndrome

Osteoporosis, postmenopausal

Piebaldism

Saethre-Chotzen syndrome



Departement Chemie und

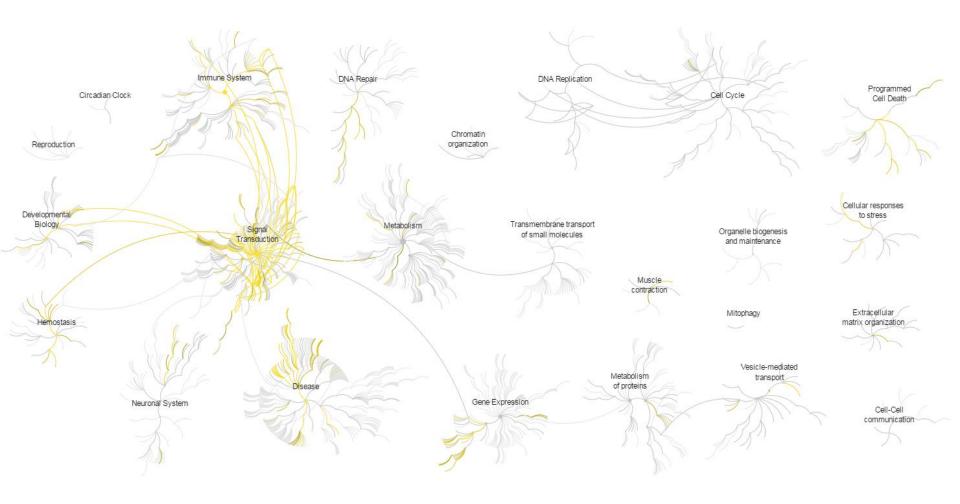














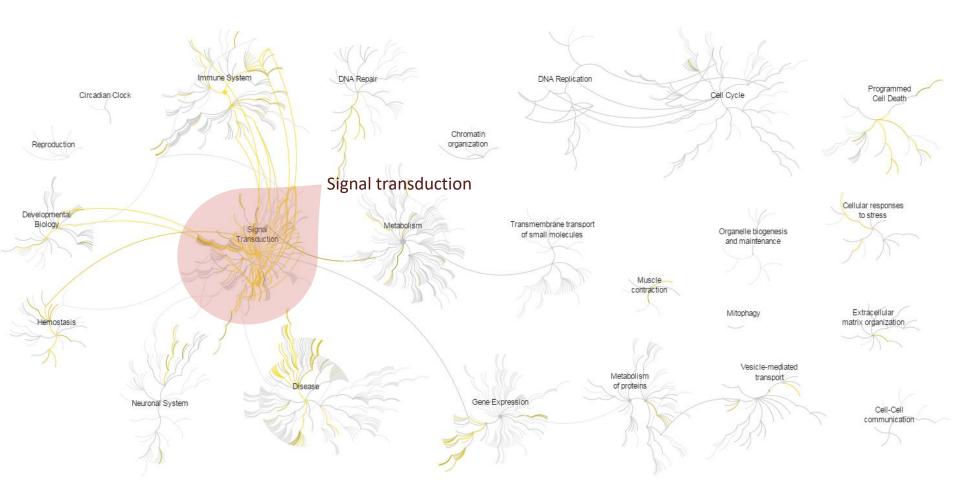














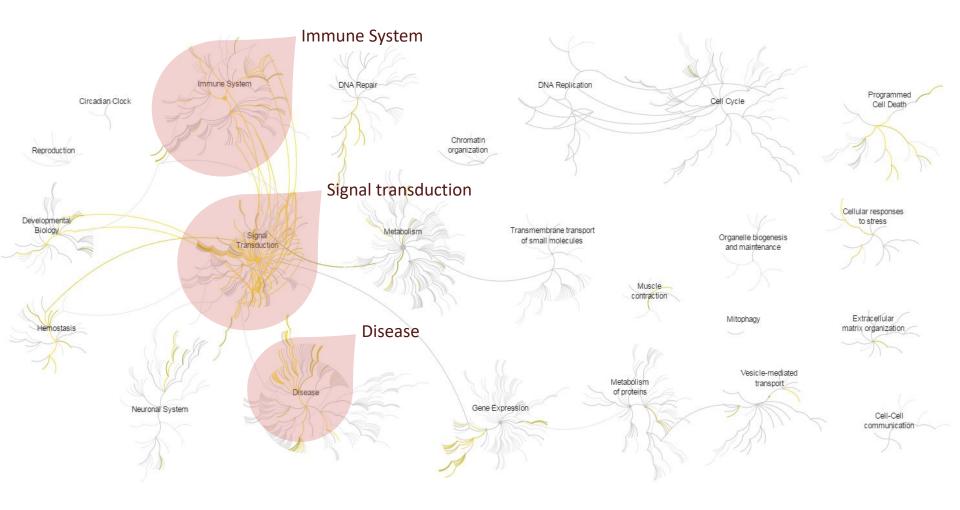














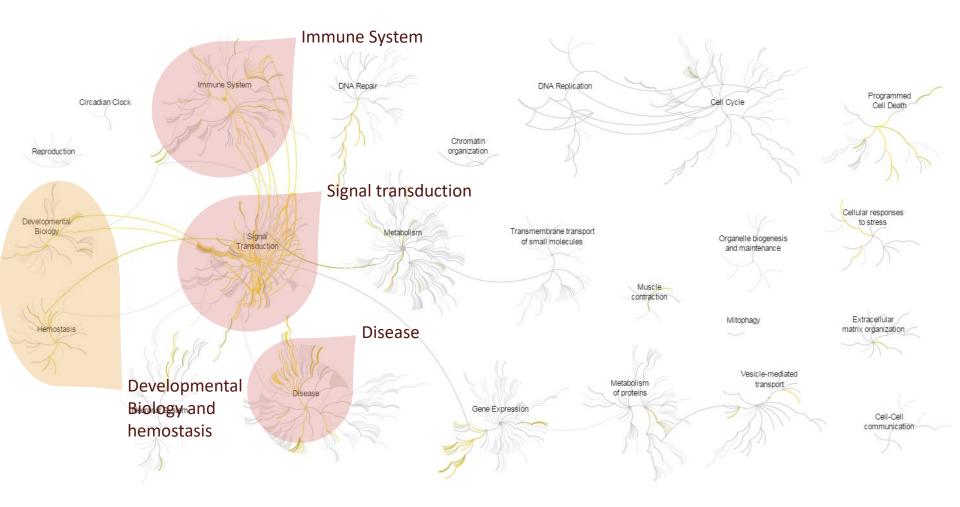










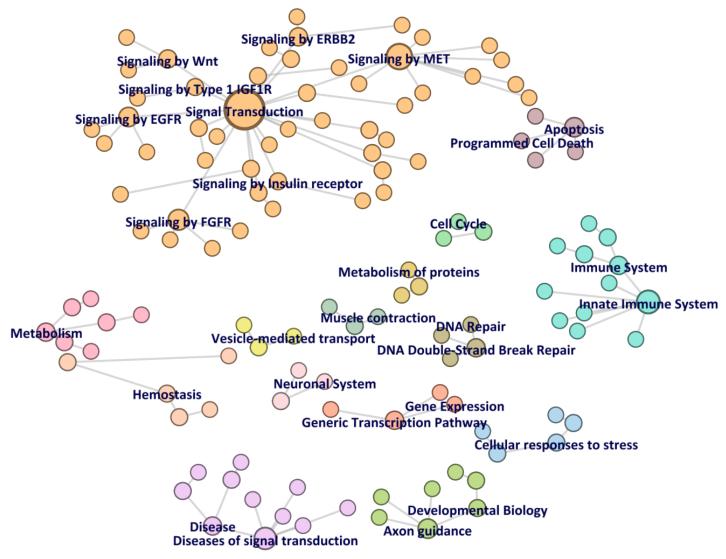










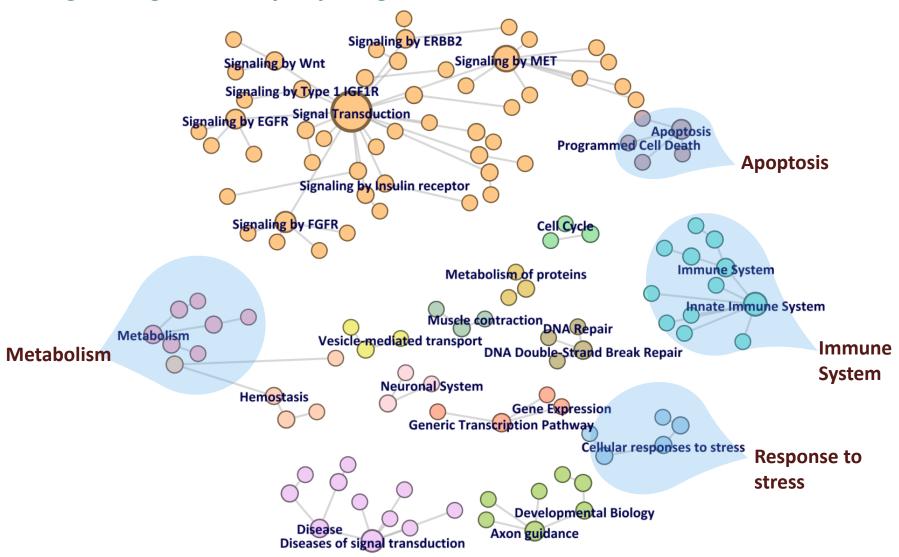










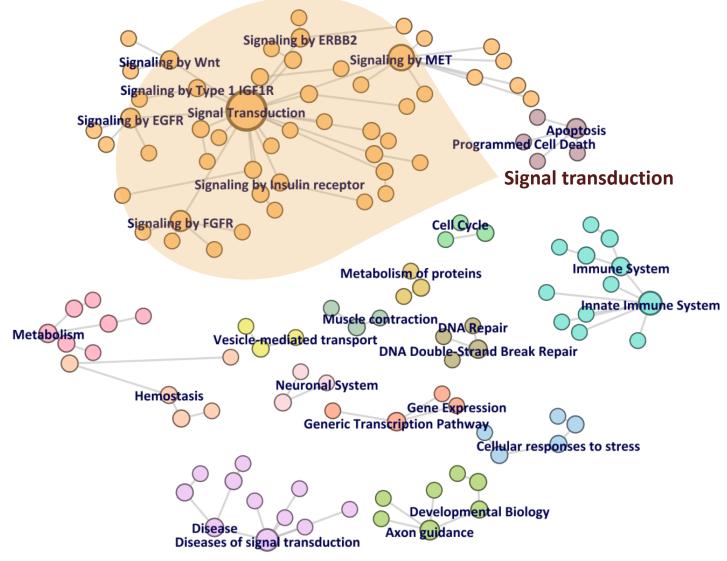










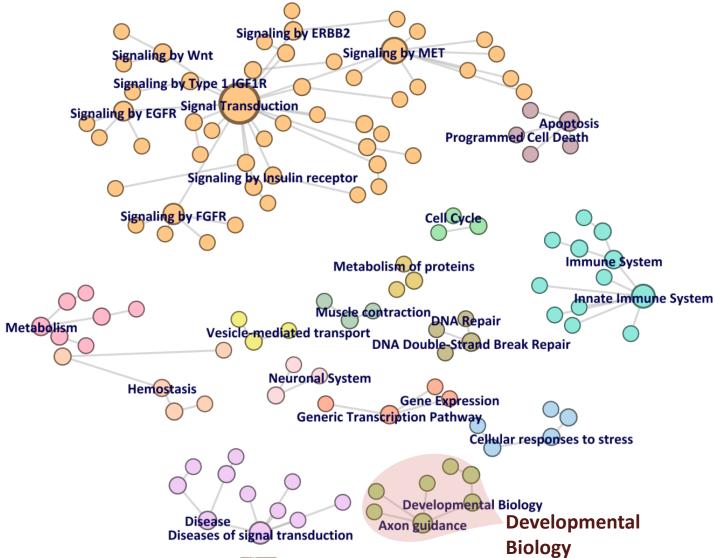








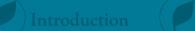






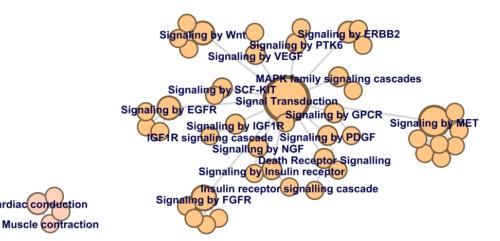


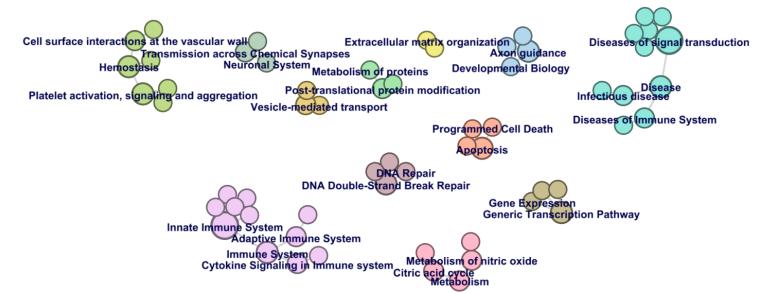
















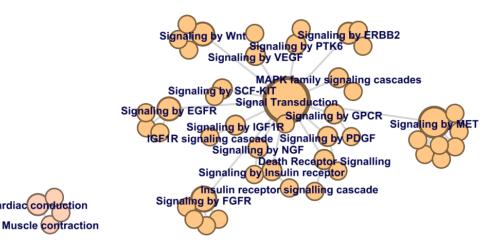
Cardiac conduction

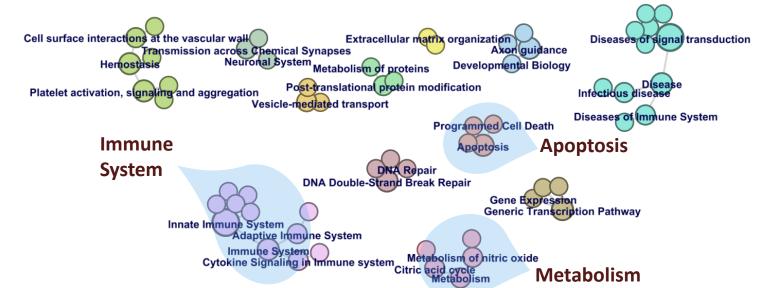
















Cardiac conduction

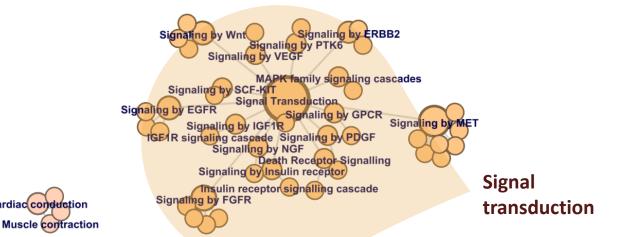


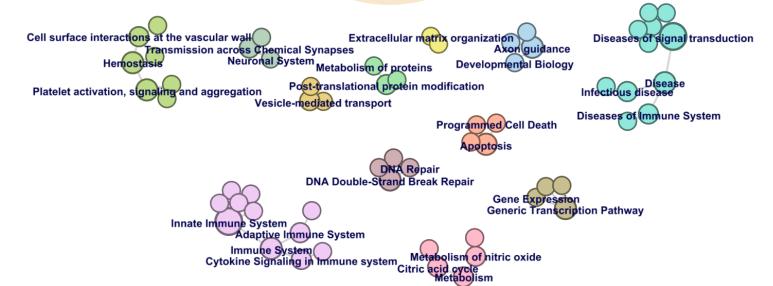










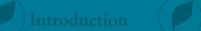






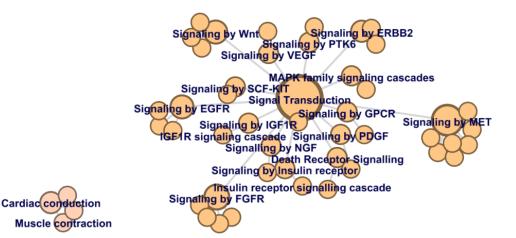
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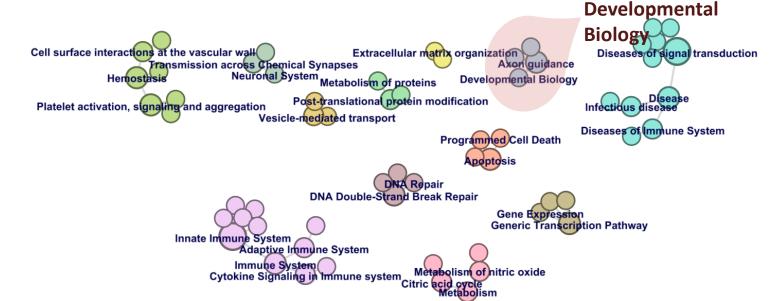














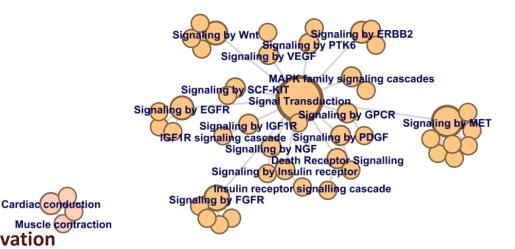












Platelet activation and aggregation

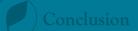
Extracellular matrix organization Cell surface interactions at the vascular wall Diseases of signal transduction Axon quidance Fransmission across Chemical Synapses Neuronal System Metabolism of proteins Hemostasis Developmental Biology Post-translationa protein modification Platelet activation, signaling and aggregation Infectious disease Vesicle-mediated transport Diseases of Immune System Programmed Cell Death **Apoptosis DNA** Repair **DNA Double-Strand Break Repair** Gene Expression Generic Transcription Pathway Innate Immune System Adaptive Immune System Immuhe System Cytokine Signaling in Immune system Metabolising Cytokine Signaling in Immune system Citric acid cycle Metabolism of nitric oxide

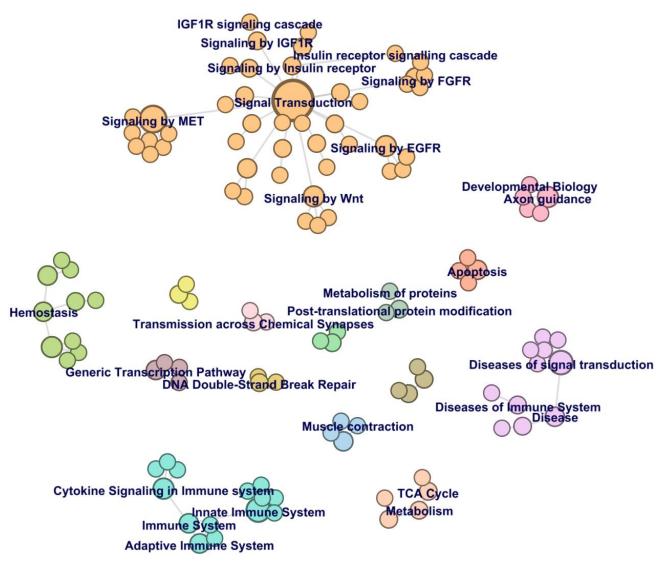










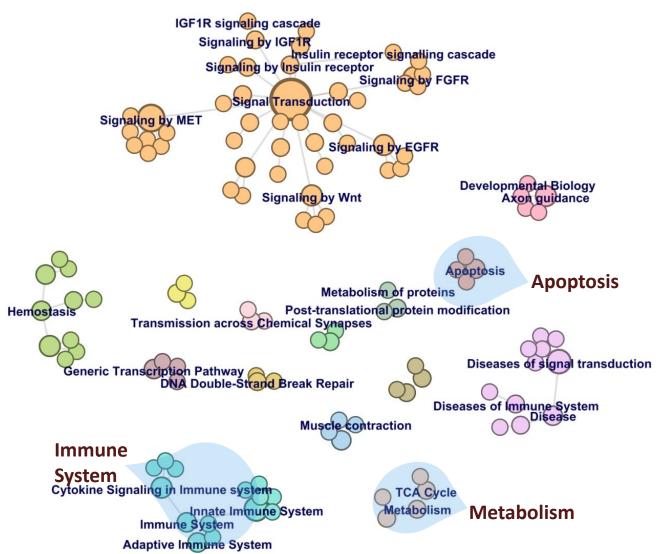














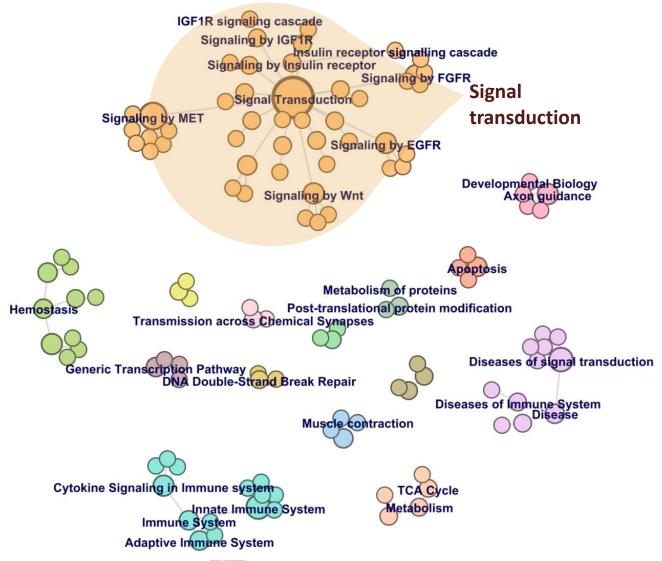












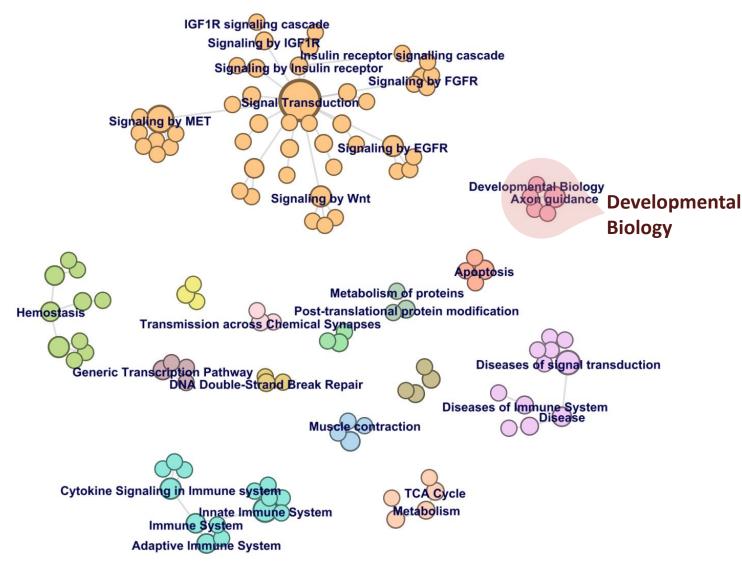














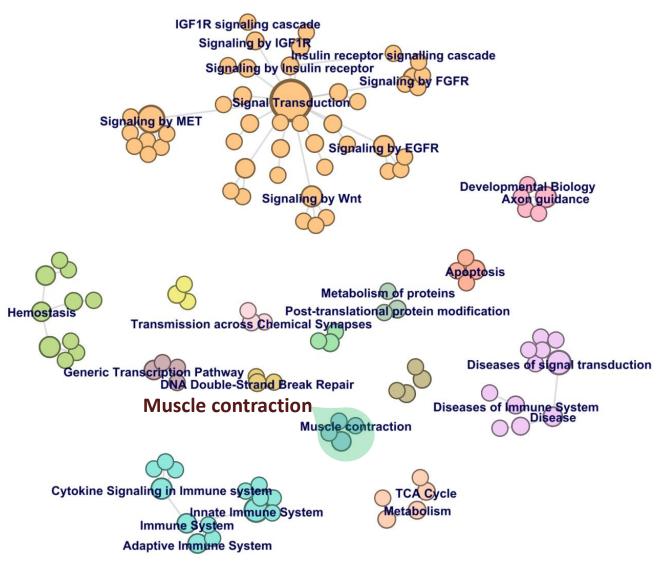


















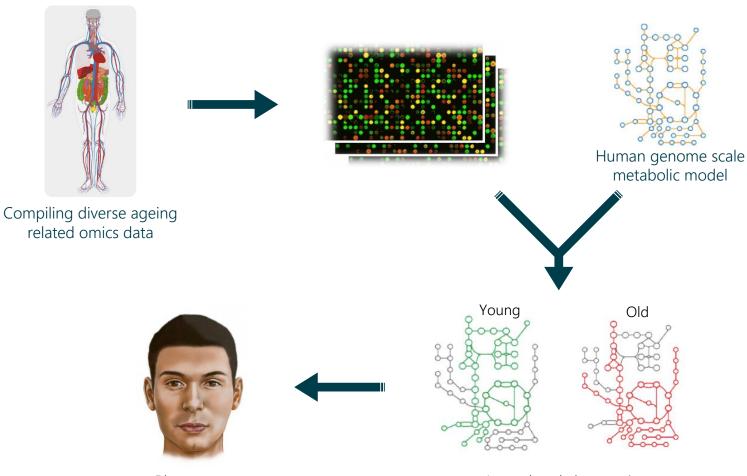








#### Age-Related Changes in Metabolic Pathways



Phenotypes

Age related changes in metabolic pathways









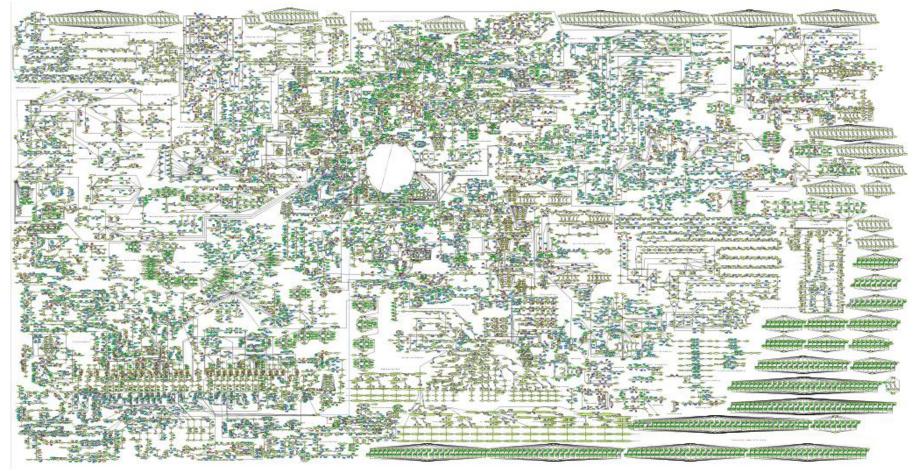






### Age-Related Changes in Metabolic Pathways

#### Human metabolic model – RECON 2









Human metabolic model – RECON 2

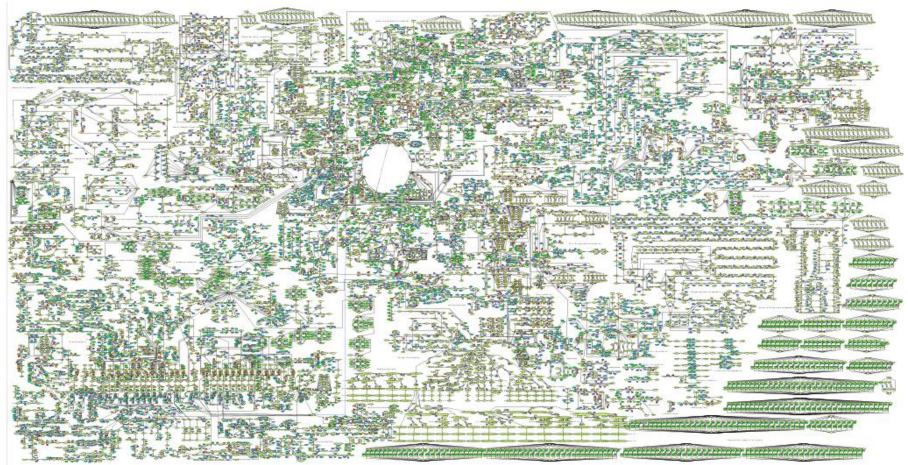






#### Age-Related Changes in Metabolic Pathways

- 7440 Reactions
- 5063 Metabolites
- 2140 Genes











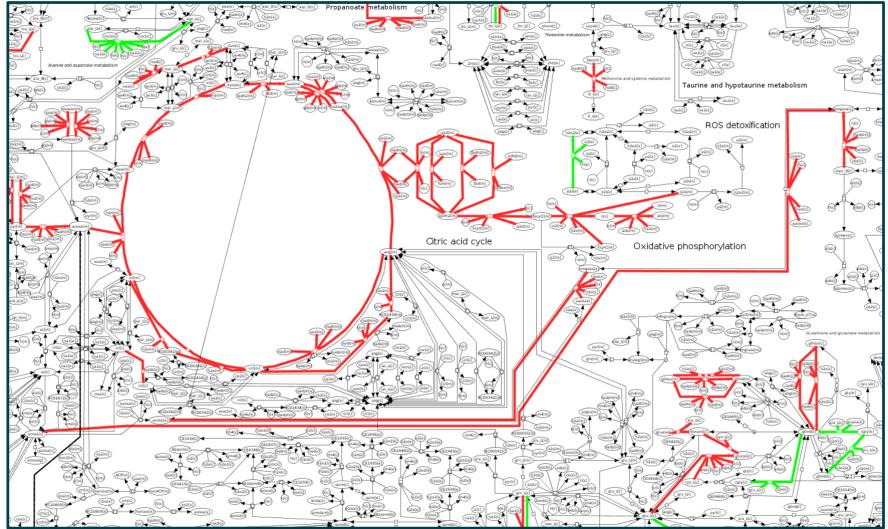




# Age-Related Changes in Metabolic Pathways

Downregulated reactions

Upregulated reactions



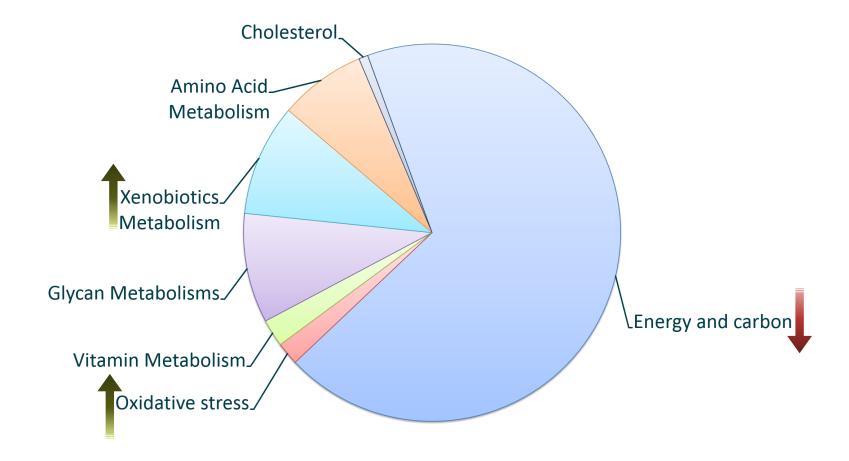








#### Age-Related Changes in Metabolic Pathways









#### **Summary**

- Our findings show ageing to be a disease of signaling. Major signaling transduction pathways were found to be closely connected to ageing and various age-related diseases.
- The analysis of human gene expression implicated alterations in metabolic pathways, particularly those related to cellular energy generation, amino acid homeostasis and xenobiotics, in the ageing process.





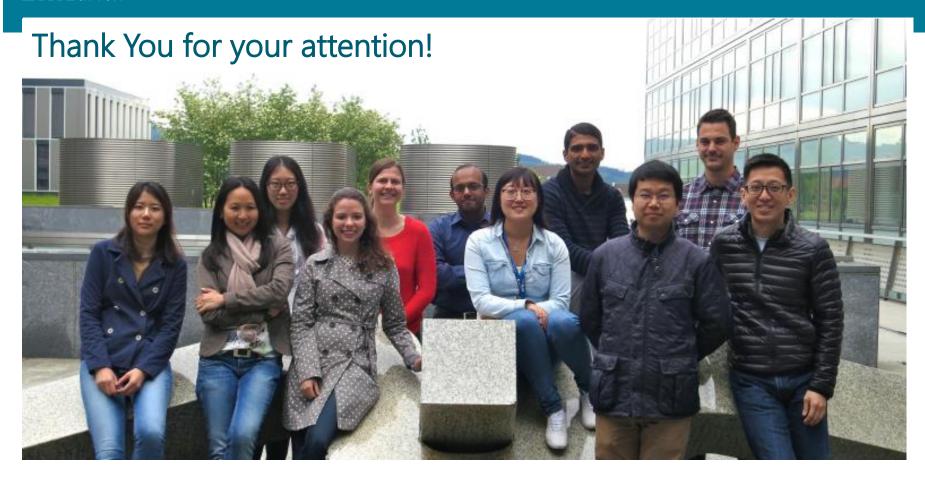
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- The analysis of human gene expression implicated alterations in metabolic pathways, particularly those related to cellular energy generation, amino acid homeostasis and xenobiotics, in the ageing process.
- We are currently working on showing that signaling errors are aberrant and damage response follows as a result of this dysregulation.
- The identification of ageing metabolic pathways is an important step in our efforts to formulate a strategy to mitigate ageing. In our continuing work, we will expand our analysis to data from dietary restricted animals, and formulate and validate metabolic targets for ageing using *C.elegans* as model organism.





#### **ETH** zürich



Dr. Lakshmi Narayanan Harini Narayanan







