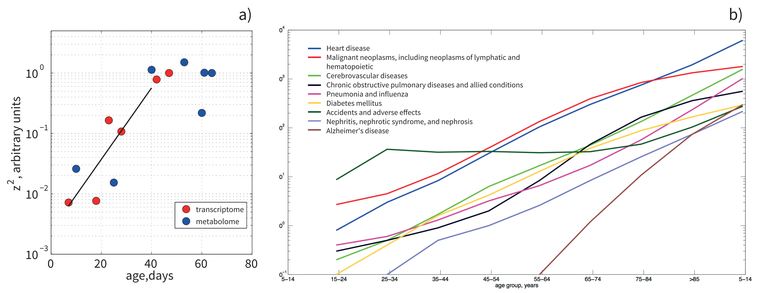
AGING TARGETS AND MARKERS IDENTIFICATION PLATFORM

We study stability properties of a generic gene regulatory network (GRN) and demonstrate that phenomenology of aging and the associated population mortality rate can be naturally described in terms of a genetic instability leading to critical dynamics of gene regulation and metabolic profiles and causing the characteristic increase in mortality rate with age as described by the Gompertz law. The model provides a systematic approach to identify therapeutic targets and biomarkers of age for future clinical trials.

For contacts: Dr. Peter Fedichev, peter.fedichev@gero.com

SCIENTIFIC EVIDENCE

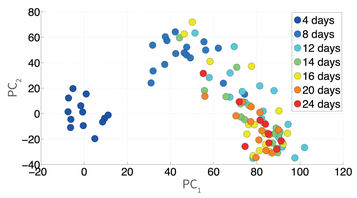
1 OUR OMIC SIGNATURES LET US IDENTIFY NOVEL THERAPEUTIC TARGETS



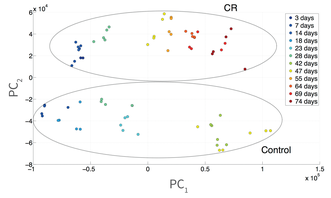
a) GERO gene signatures are directly related to all causes mortality, rather than to calendar age (see the figure, the relation between the inferred, ***z***, and age in transcriptomic and metabolomic data from works [2] and [3]). The model has been developed into powerful tools for novel therapeutic targets inference with the aim to reduce mortality, delay aging and onset of **b)** age-related diseases (Log plot of mortality (H. sapiens). Data from [4])

2 CRITICAL DYNAMICS OF GENE EXPRESSION IS BEHIND AGE-RELATED CHANGES IN OMICS DATA AND AGE-DEPENDENT ALL CAUSES MORTALITY INCREASE

We show that aging has a strong deterministic component (aging direction), which can be naturally associated with a part of a development program, leading to death of an organism. Since mortality in humans is mostly associated with age-related diseases, we support the idea of aging being the driving force behind the development of major diseases.



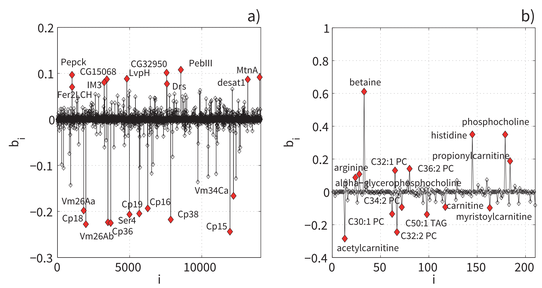
a) Principal component analysis of aging worm transcriptomes from [1]



b) Principal component analysis of aging D.melanogaster transcriptiomes from [2]

3 BIOMARKERS OF ALL CAUSES MORTALITY (AKA AGING) IN OMICS DATA

WE DEVELOPED A METHOD FOR IDENTIFICATION THE BIOMARKERS OF AGING AS GENES OR METABOLITES CHANGING ALONG WITH THE MORTALITY FROM A LIMITED NUMBER OF SAMPLES (BIG DATA LIMIT)



Basic biological evidence for the presented stochastic model of aging:

a) Components of the aging direction for D. melanogaster, analysis of age-associated changes in transcriptional profiles only [2]. Peaks correspond to the values of the components of the aging direction for every gene in the dataset.

b) Components of the aging direction for D. melanogaster, computed using the levels of targeted metabolites only [3].

PHARMA'S CHALLENGES

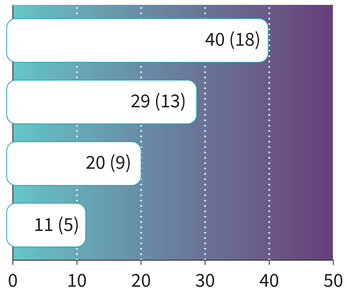
BIOTECHNOLOGY ASSAYS ARE PERFORMED QUICKLY, BUT DISEASES EVOLVE SLOWLY:

- Biochemical assays - hours
- Cell assays - days
- Preclinical efficacy - weeks
- Clinical trials - months-years
- Post-approval efficacy - years

TARGET IDENTIFICATION RELATED RISKS UNDERMINE DRUG DISCOVERY EFFORTS

REASONS FOR LACK OF CLINICAL EFFICACY

- Target linkage to disease not established or no validated models available
- Dose limited by compound characteristics or tissue exposure not established
- Indication selected does not fit strongest preclinical evidence
- Evidence from previous phase not robust enough



Percentage of all reported reasons (total number of projects: 28)

" ... the proportion of target-related safety closures rose substantially in the clinical phase and was responsible for almost half of the safety-related project closures...

...The next highest cause of project closure overall was a lack of efficacy in the chosen disease indication..."

from D. Cook et al, Nat. Rev. Drug Discovery, 419 (13), 2014

HOW TO DEVELOP REMEDIES ON DIFFERENT SCALES, AND ARE THERE "ROBUST" TARGETS?

SOLUTIONS

Our technology serves as a collaboration environment for analysis of the provided omics data using Gero proprietary computational platform to identify new targets against aging and age-related diseases and biomarkers of aging. This results in the creation of new therapies, surrogate and other biomarkers, age-related diseases treatment and diagnostics methods.

GERO DESIGNS 5 TYPES OF SOLUTIONS THAT ARE CREATED USING COMPANY'S OWN RESOURCES, FOR FURTHER CO-DEVELOPMENT OR OUT-LICENSING IN BIOTECH/PHARMA INDUSTRY:

1. New target (regulator of aging) identification
2. Biological age and rate of aging in biological samples
3. Biological age and rate of aging in motion activity
4. Biological signals processing in Big Data limit
5. Screening system for geroprotectors validation

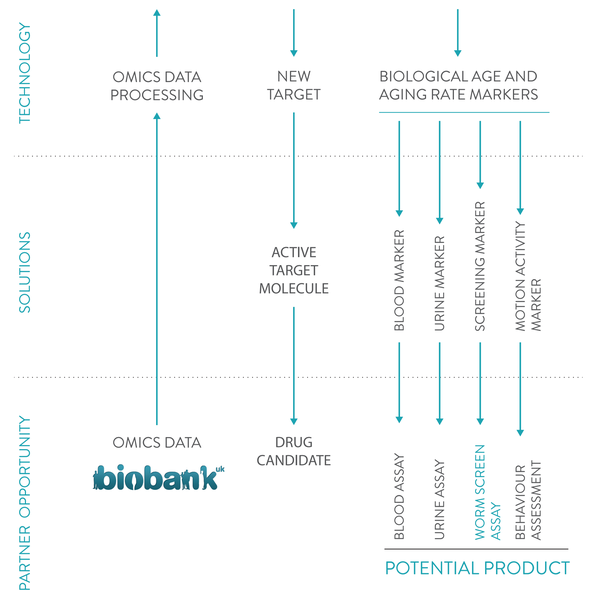
IMPLEMENTATION

OUR SOLUTIONS ARE USEFUL FOR:

- **Biotech and Pharma**
  - novel therapeutic targets and markers
  - novel drugs and combination
  - drug repositioning
  - chronic toxicity assessment
  - personalized medicine
- **Test systems providers** (medical data suppliers)
- **Insurance companies**

TECHNOLOGY SOLUTIONS

TARGET AND MARKER IDENTIFICATION PLATFORM



PARTNER OPPORTUNITY COLLABORATIONS

We work with academic and commercial longitudinal omics data providers.

We are looking to collaborate with academics, omics-data providers, assays and diagnostic kits developers, and biotech and pharma companies to accelerate the development of biomarkers of aging and new therapies for age-related diseases.

We are developing a new treatment approach against aging and age-related diseases targeting new regulators of aging.

REFERENCES

[0] D Podolskiy, et al. "Critical dynamics of gene networks is a mechanism behind ageing and Gompertz law" arXiv preprint arXiv:1502.04307
[1] Golden, Tamara R., et al. "Age-related behaviors have distinct transcriptional pro les in Caenorhabditis elegans." Aging cell 7.6 (2008): 850-865.
[2] Pletcher, Scott D., et al. "Genome-Wide Transcript Profiles in Aging and Calorically Restricted Drosophila melanogaster." Current Biology 12.9 (2002): 712-723.
[3] Avanesov, A. S. et al. Age-and diet-associated metabolome remodeling characterizes the aging process driven by damage accumulation. eLife 3 (2014).
[4] Xu, Jiaquan, et al. "Deaths: final data for 2007." National vital statistics reports58.19 (2010): 1-136.
[5] Kogan, Valeria, et al. "Stability analysis of a model gene network links aging, stress resistance, and negligible senescence." Scientific Reports 5, Article number: 13589 (2015) 10.1038.
[6] Horvath, Steve. "DNA methylation age of human tissues and cell types." Genome biology 14.10 (2013): R1
[7] Belsky, Daniel W., et al. "Quantification of biological aging in young adults." Proceedings of the National Academy of Sciences 112.30 (2015): E4104-E4110.

DRUG DISCOVERY PROCESS: IDENTIFY TARGETS → IDENTIFY BIOMARKERS → SCREENING → DRUG CANDIDATE → PATIENT STRATIFICATION → CLINICAL EVIDENCE → PERSONALIZED DIAGNOSTICS

OUR SOLUTIONS: 1 4 | 2 4 | 5 | 2 | 2 | 3

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