Genes, ambiente y envejecimiento celular

Alexander de Luna
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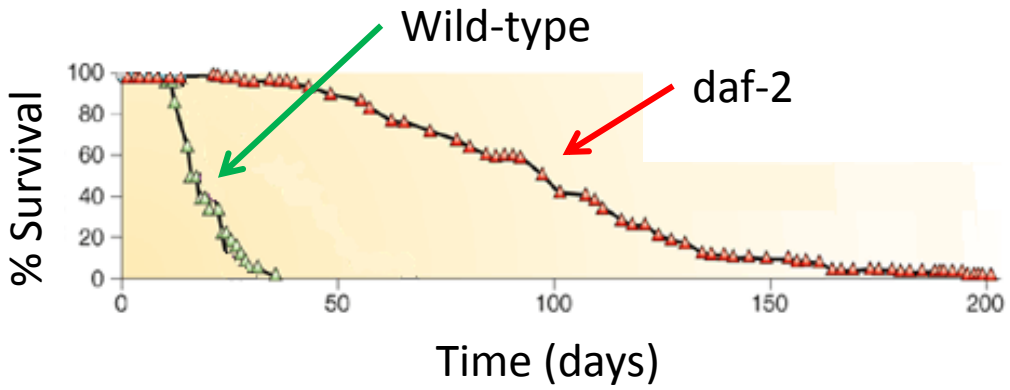
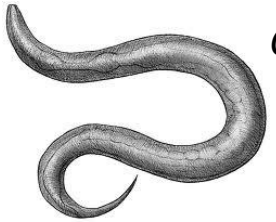
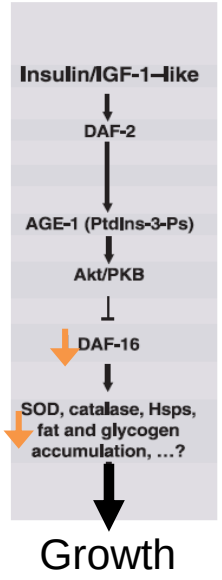
The aging process is controlled by **conserved genes** and pathways





C. elegans

Kenyon et al. *Nature* 1993



- What genes and cellular pathways influence aging and longevity?

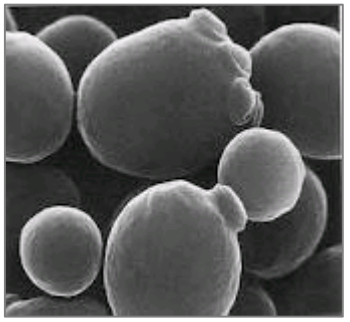
- How are different genetic aging factors integrated to one another?

- Which genes and pathways mediate lifespan extension by dietary restriction?

Yeast is one of the most **useful model** organisms used in aging research

Replicative lifespan (RLS):
Number of mitotic divisions

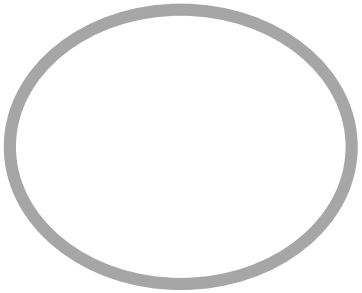
n **=** Replicative lifespan

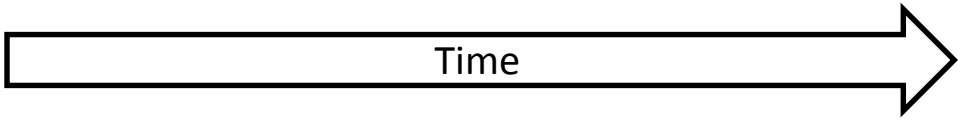


S. cerevisiae

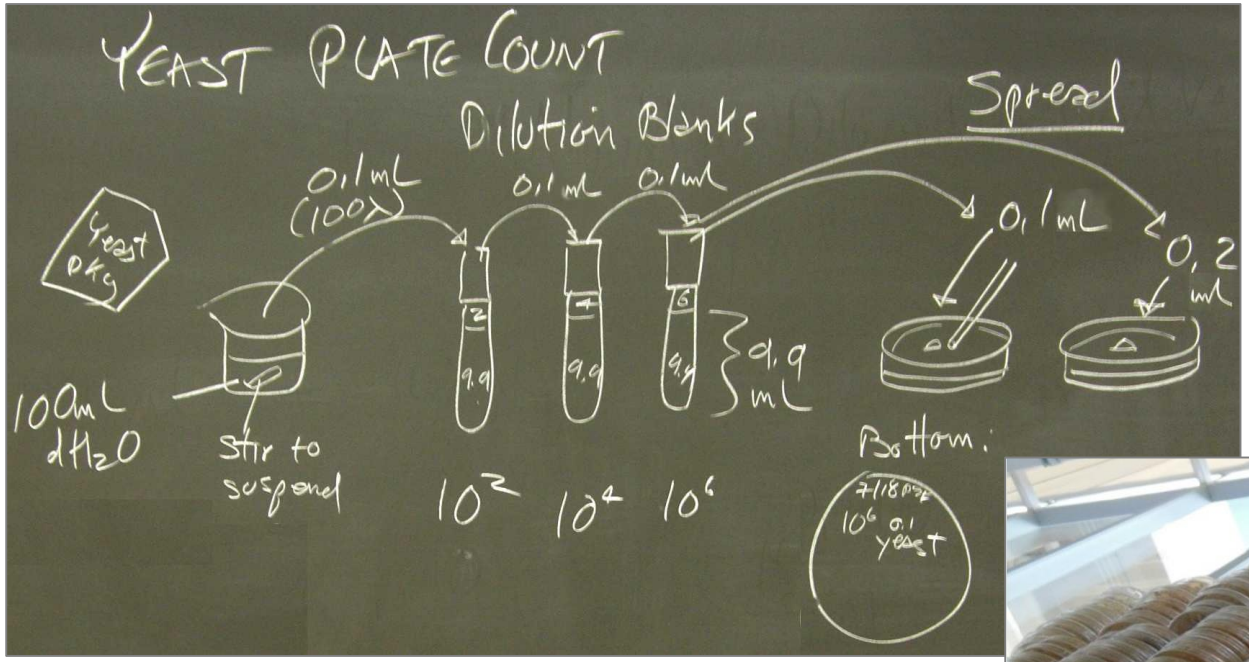
Chronological lifespan (CLS):
Number of days viable in stationary phase

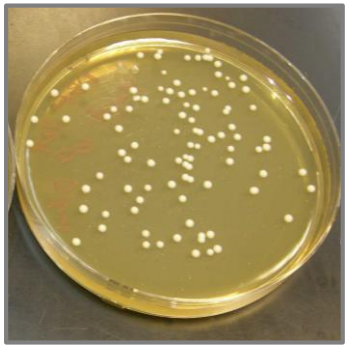
t **=** Chronological lifespan



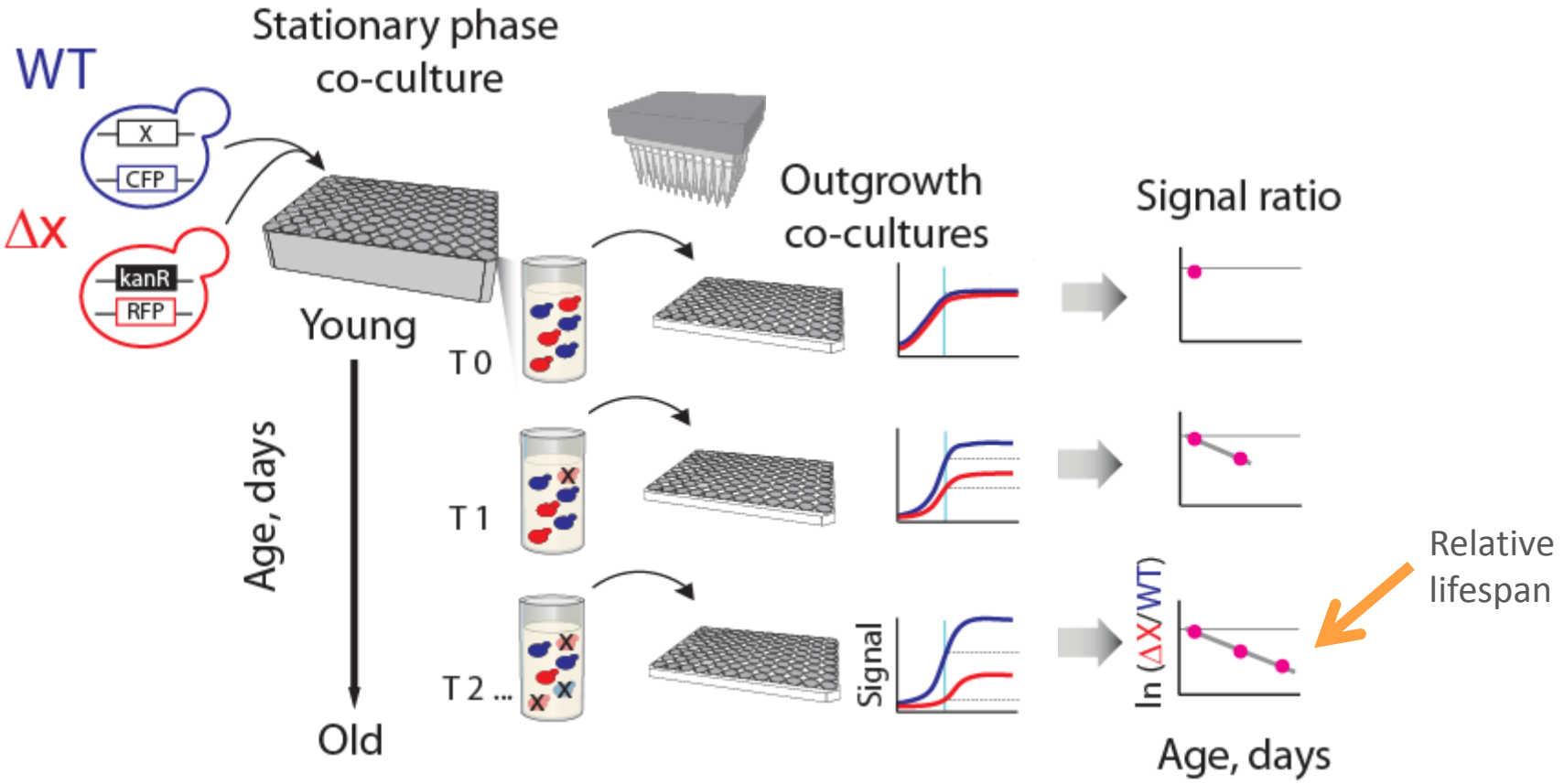


Measuring the chronological lifespan of yeast is a **laborious procedure**



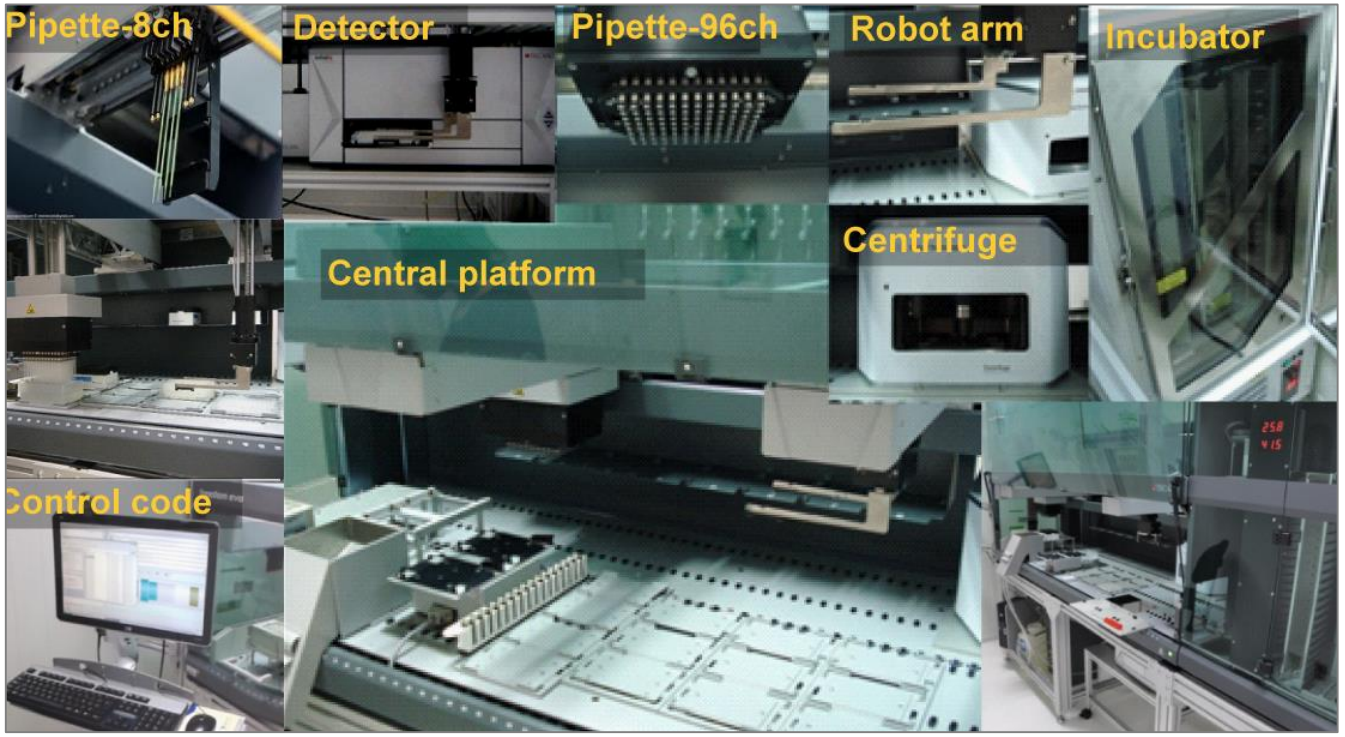


We have introduced a high-resolution strategy to characterize the **chronological lifespan** of yeast



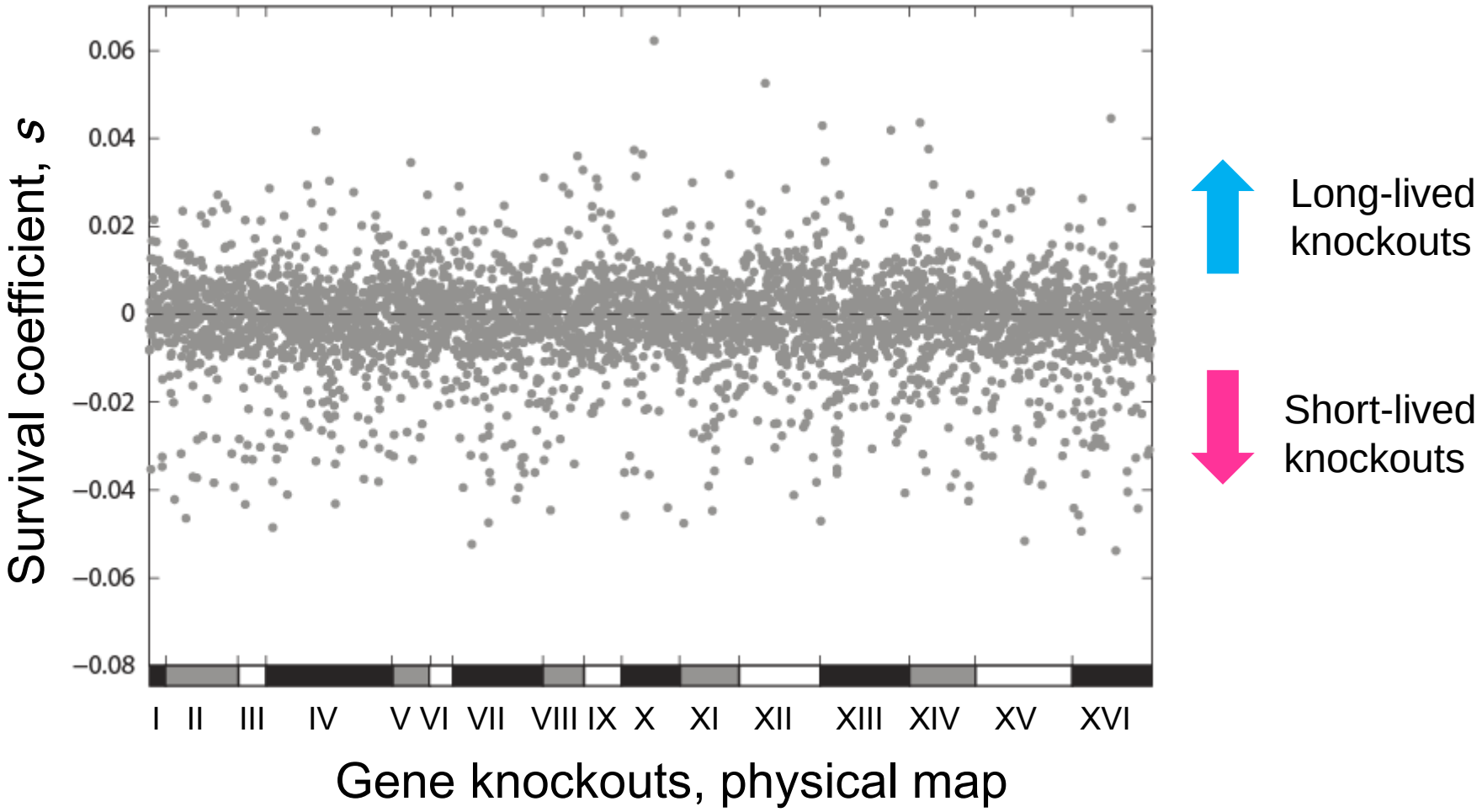
Garay et al. *PLoS Genetics* 2014

We use an **automated cell-assay** station to scale-up our genetic analyses of aging in yeast

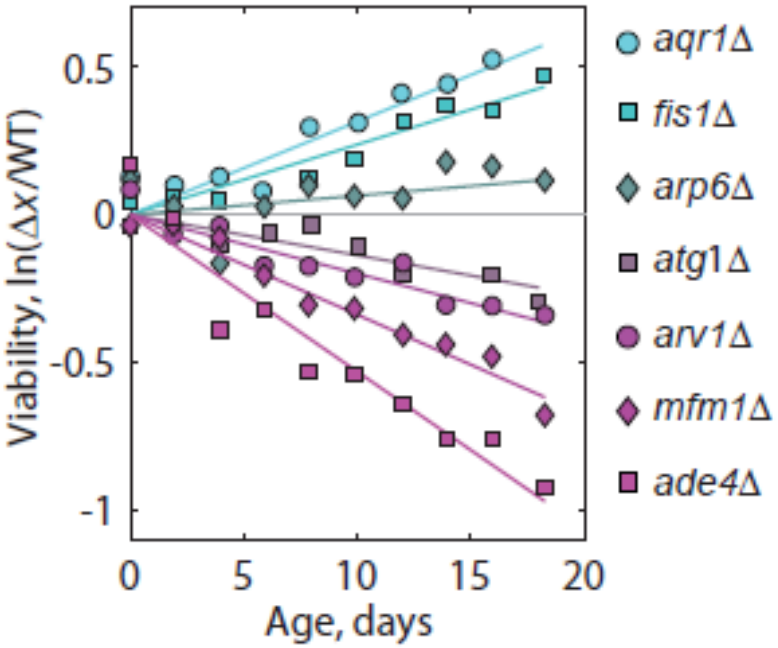


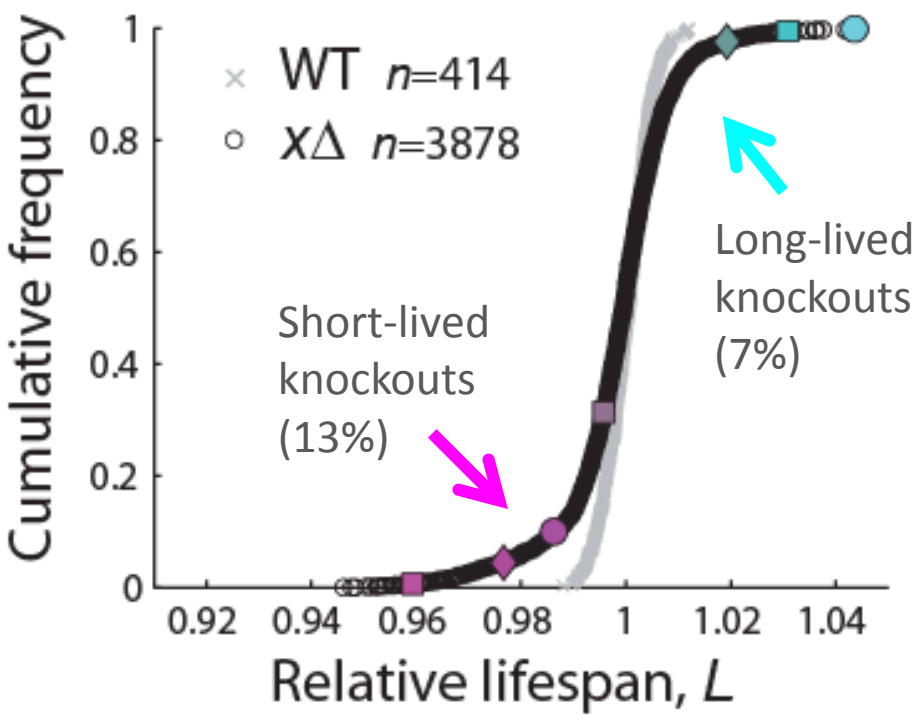
We use an **automated cell-assay** station to scale-up our genetic analyses of aging in yeast

We screened the entire **yeast genome** for lifespan phenotypes

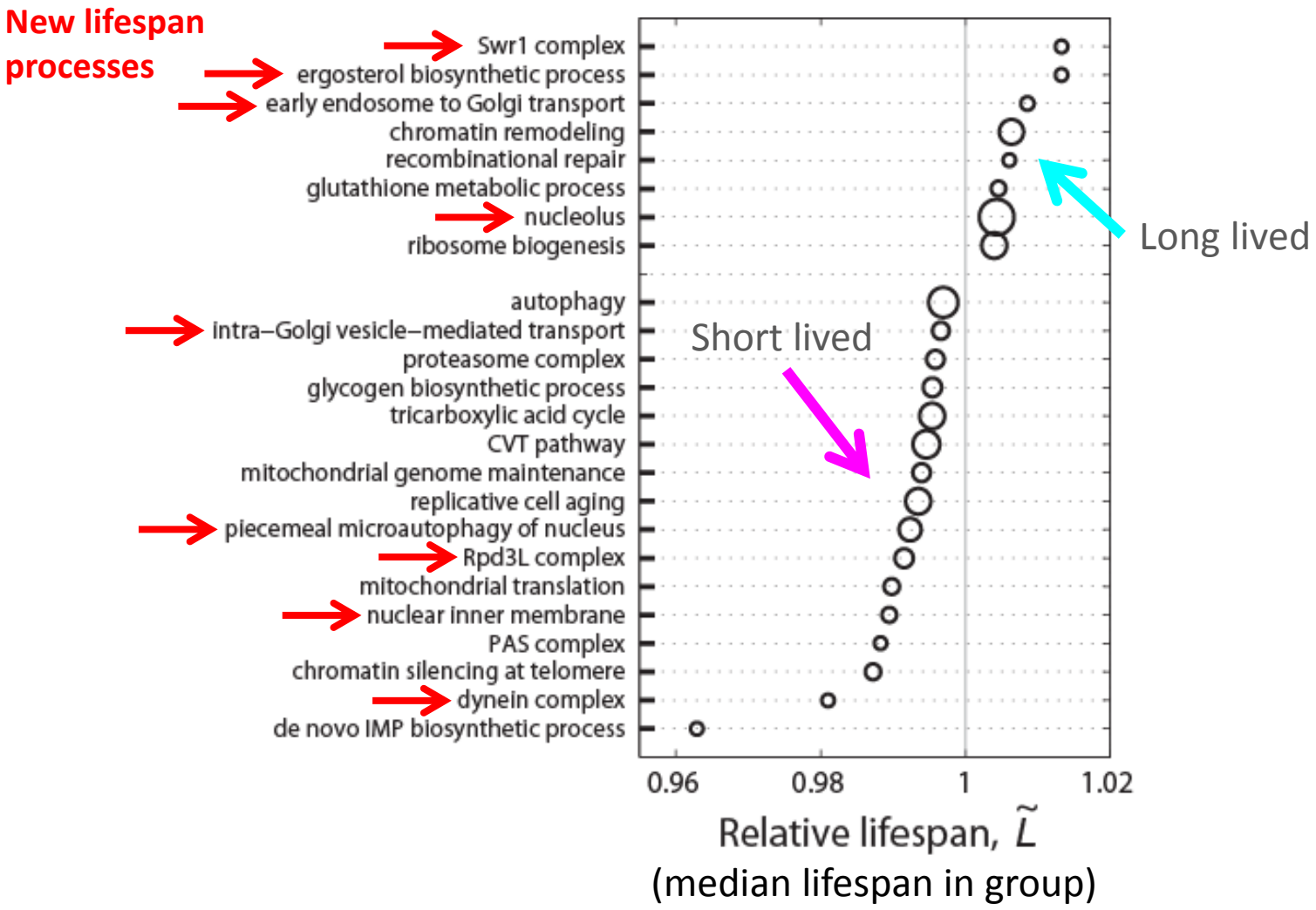


Our large-scale **single-knockout** screen reveals that a substantial fraction of the genome influences lifespan

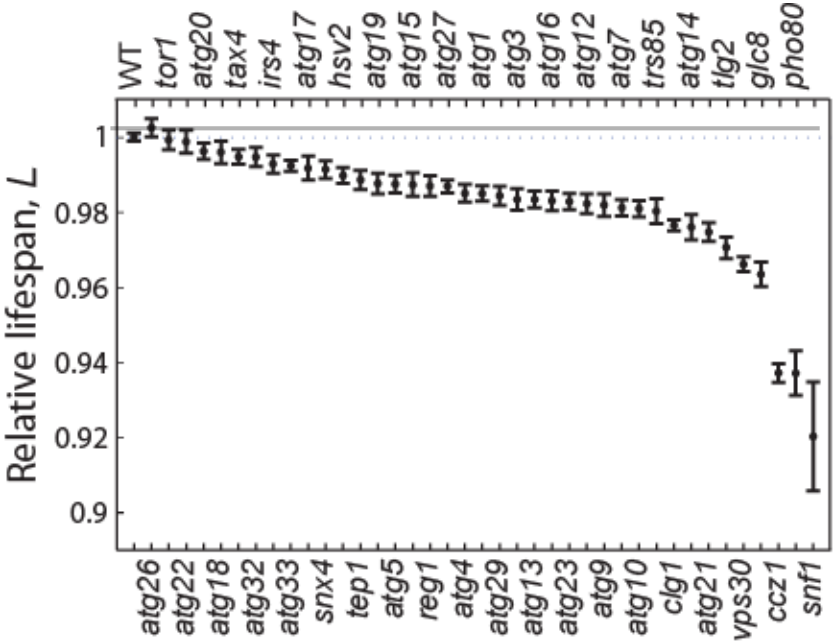




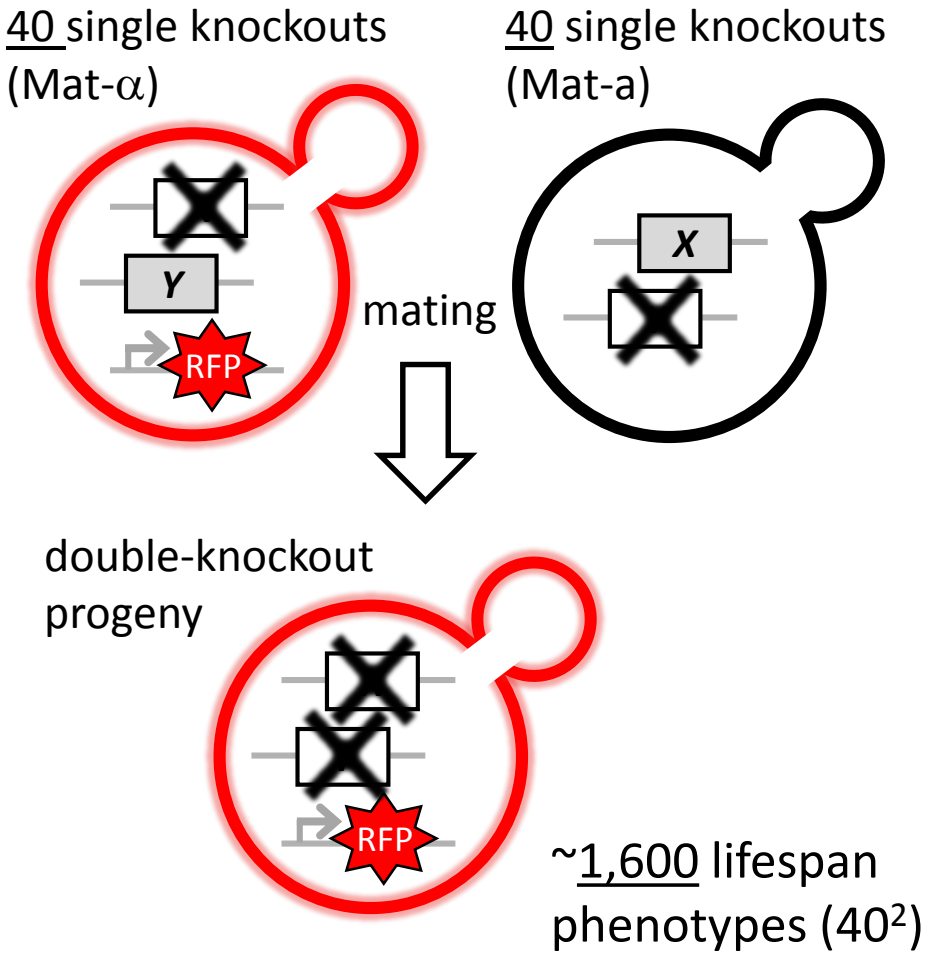
We identified **novel processes** that influence lifespan



The systematic characterization of **double knockouts** informs on functional gene associations

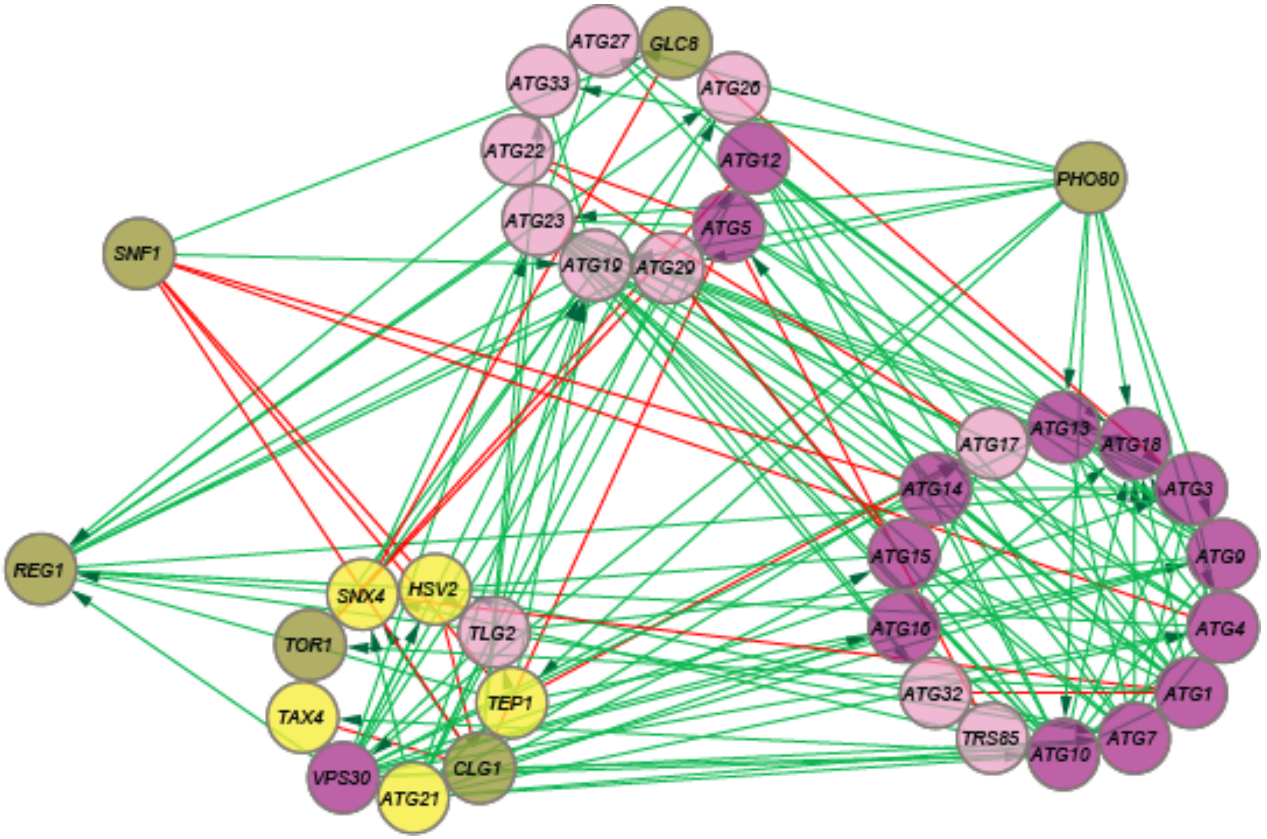


40 genes of the autophagy machinery (or related to)



A genetic interaction network describes **functional associations** within and between longevity pathways

- Core ATG
- CVT pathway
- PIP
- Signaling



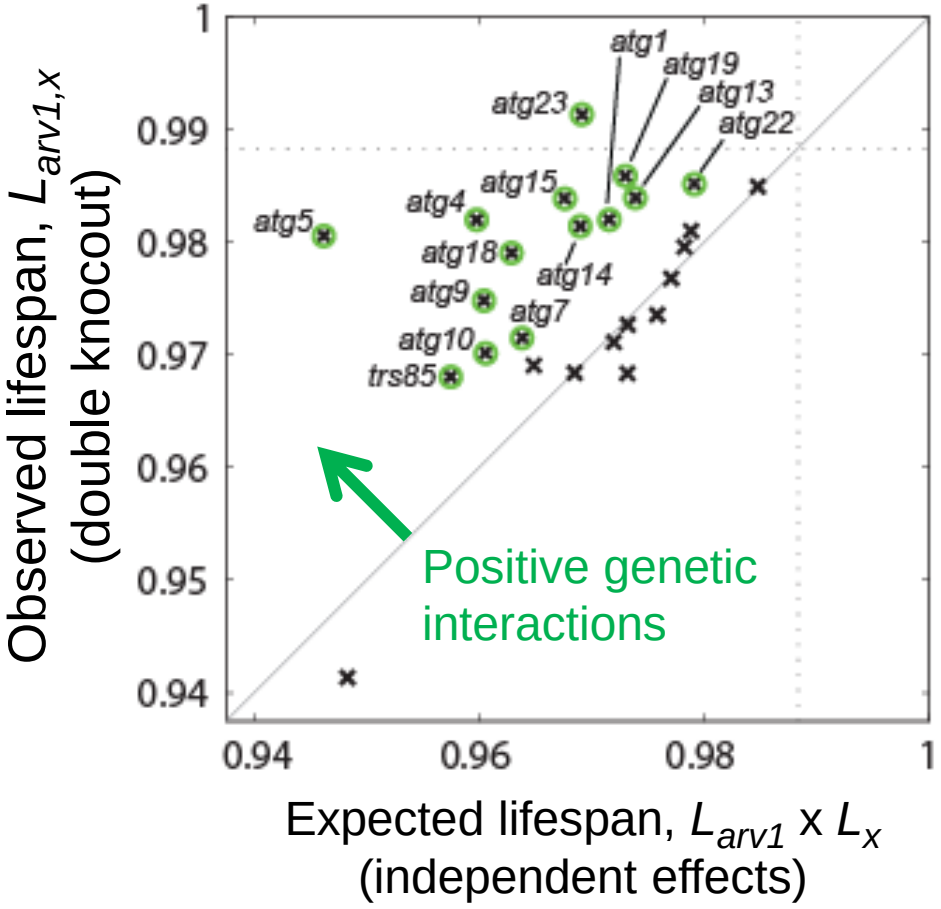
Negative genetic interaction

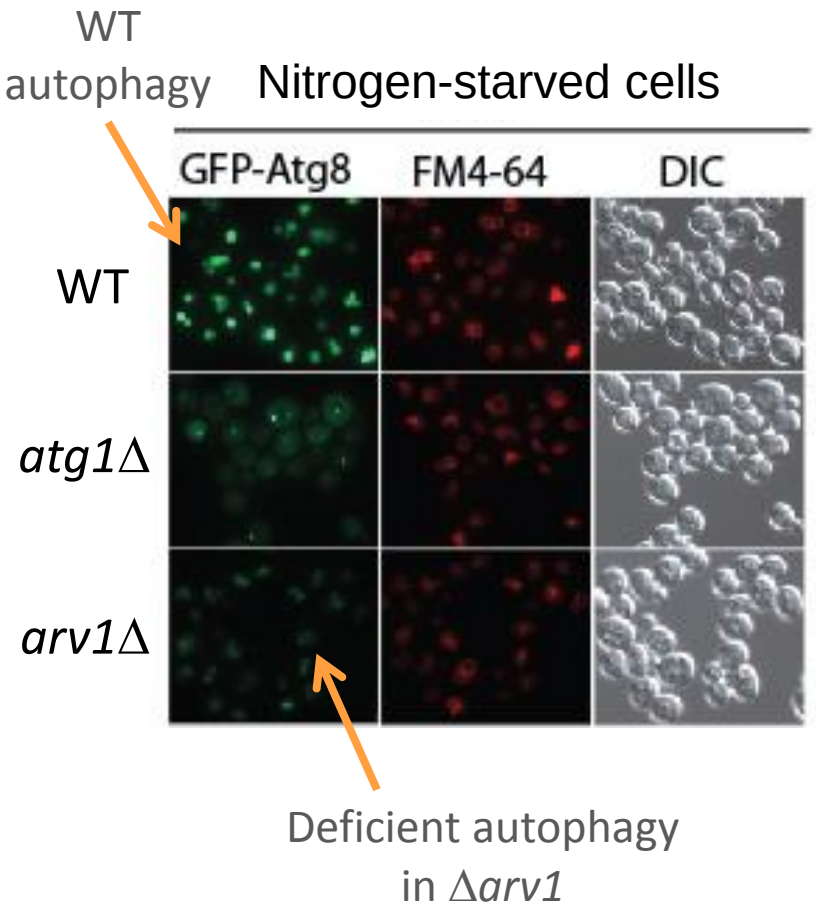
Positive genetic interaction

In our pipeline: A pairwise interaction map of ~160 genes generated with >22,000 lifespan phenotypes

The novel longevity factor **Arv1 extends lifespan** by mediating autophagy function

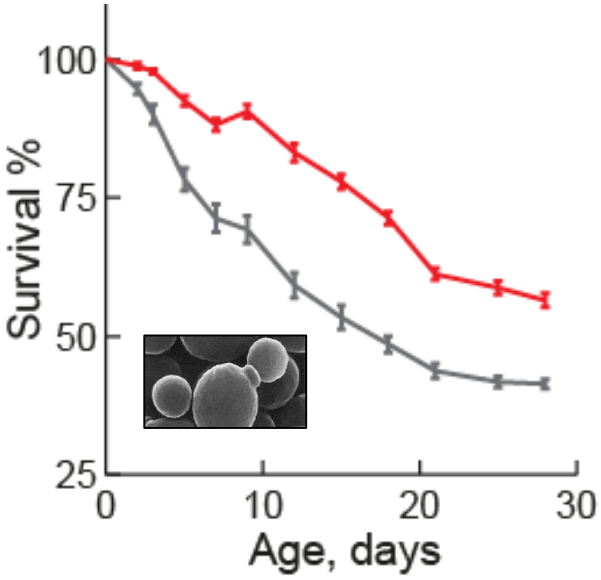
*arv1*Δ,*atgX*Δ double knockouts

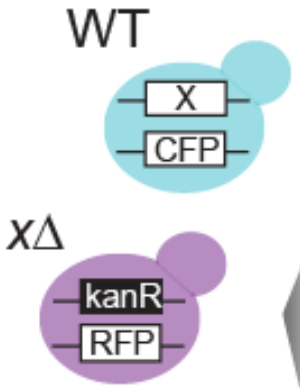


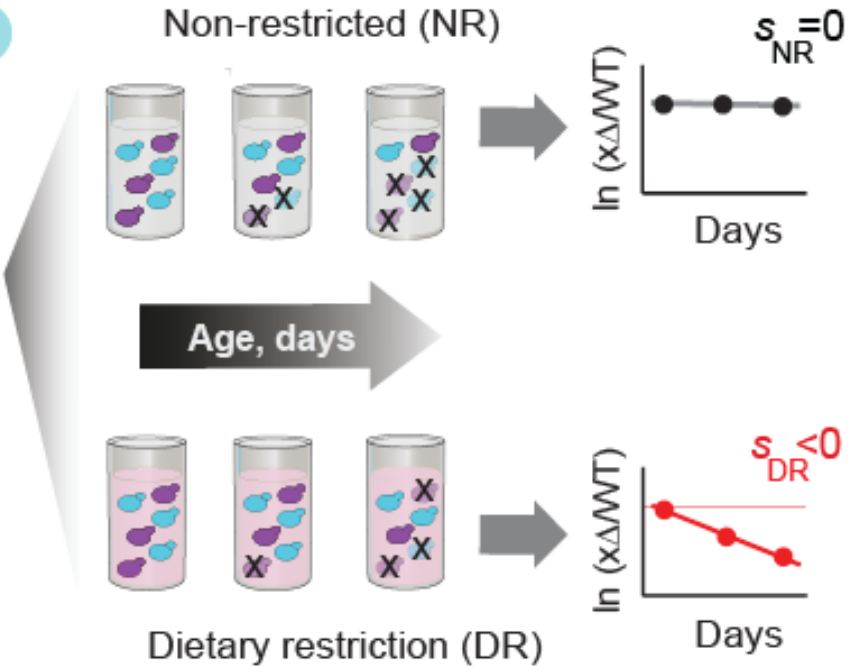


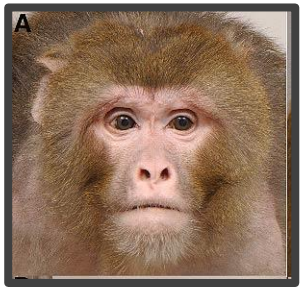
x

Gene-environment interactions inform on mechanisms of lifespan extension by **dietary restriction**

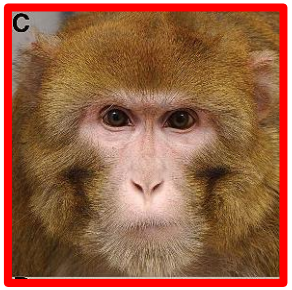








Non-restricted

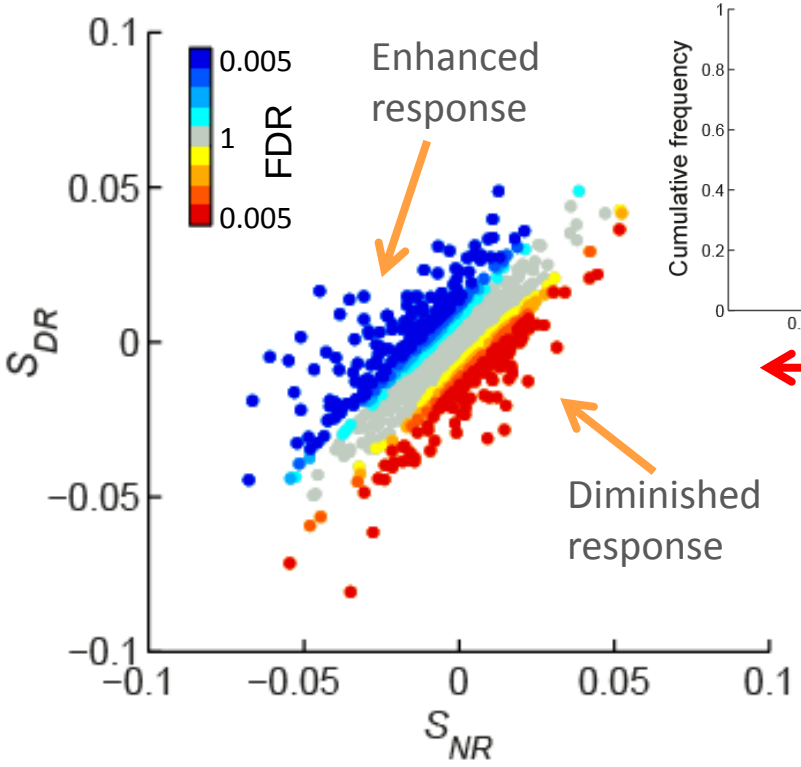


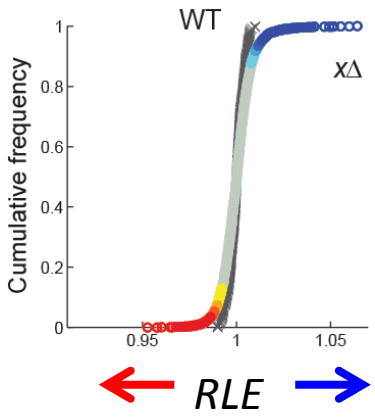
Dietary restriction

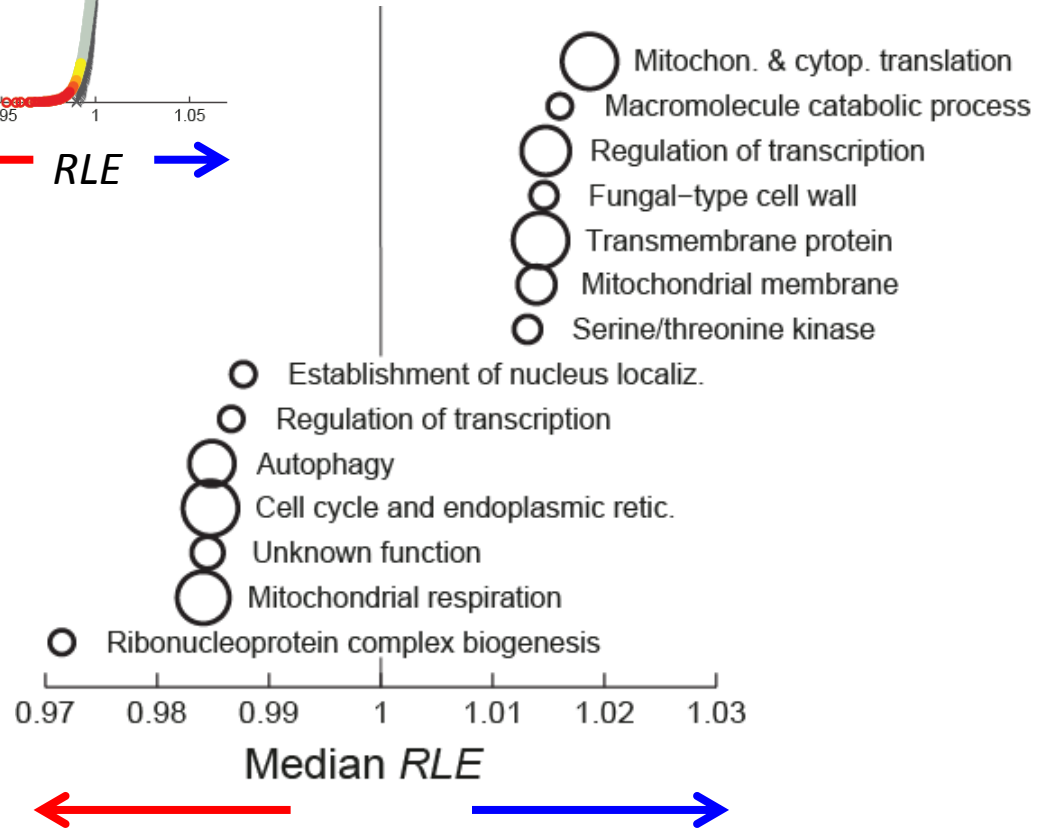
Age: 27yrs

Colman et al. *Science* 2014

We revealed **novel mechanisms** of cellular-lifespan extension by dietary restriction

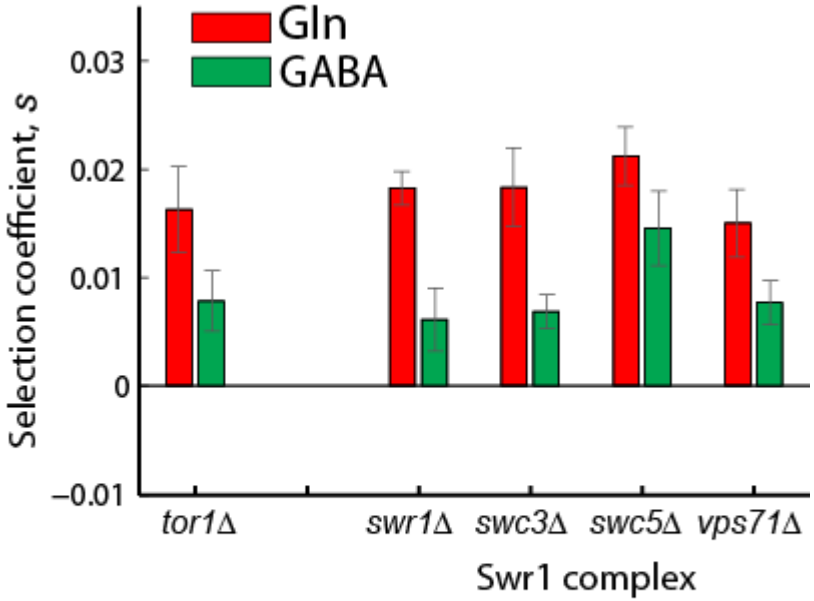


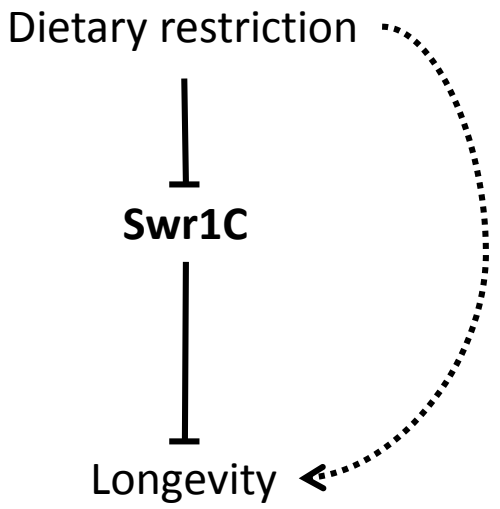




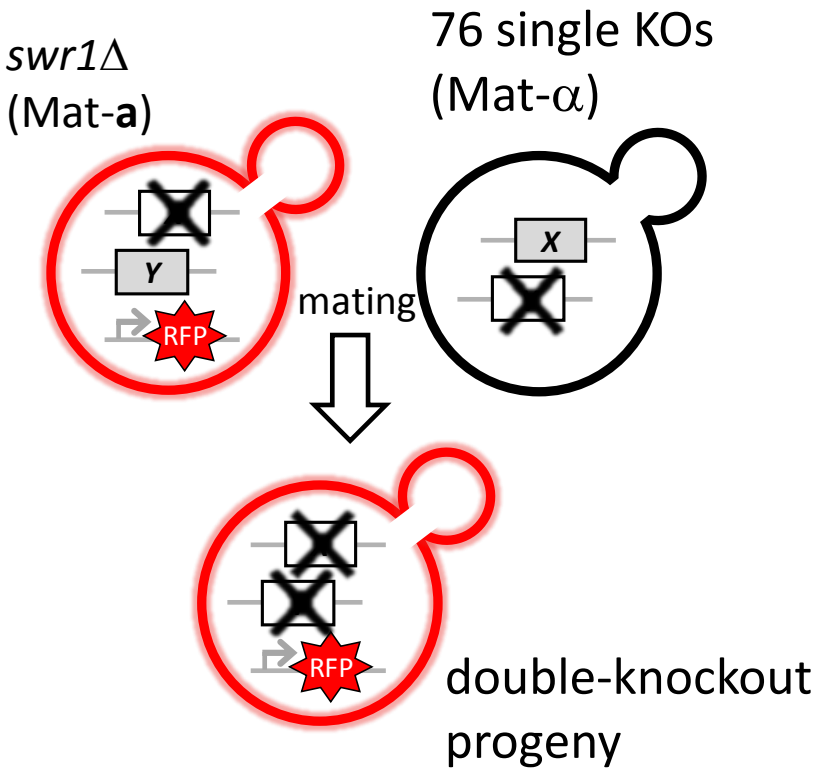
Campos *et al*. in prep.

The new longevity factor **Swr1C** mediates lifespan extension by dietary restriction





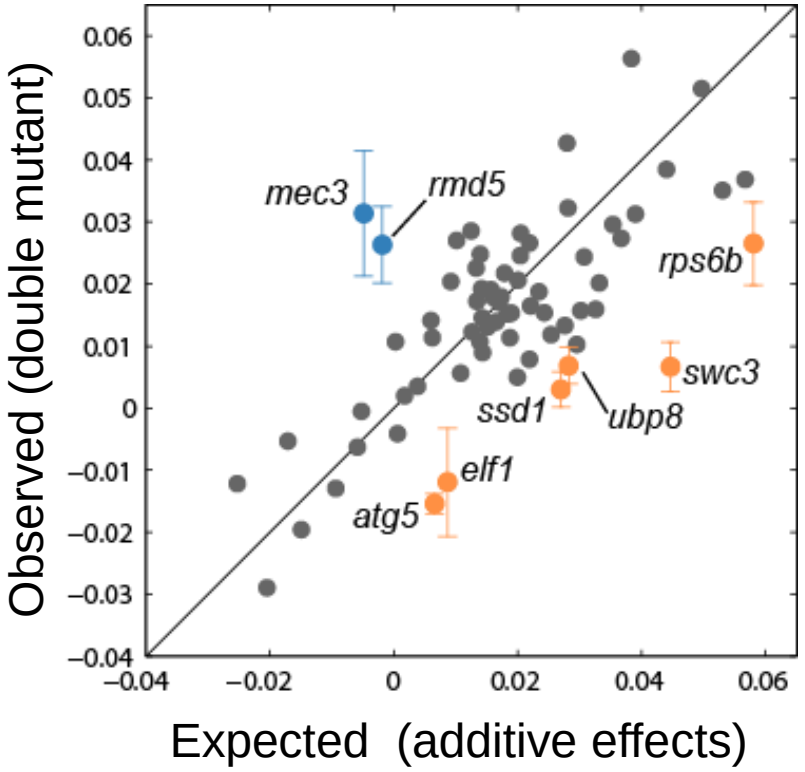
We used **double-mutant analysis** to explore the associations of Swr1C with other aging factors



$$\varepsilon = s_{xy} - (s_x + s_y)$$

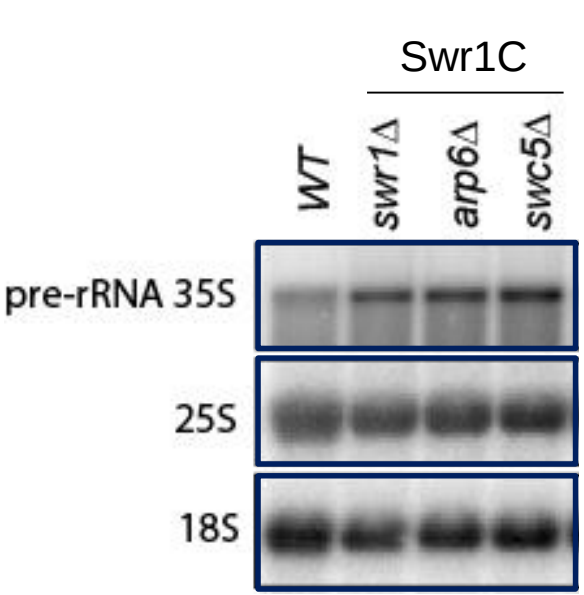
observed expected

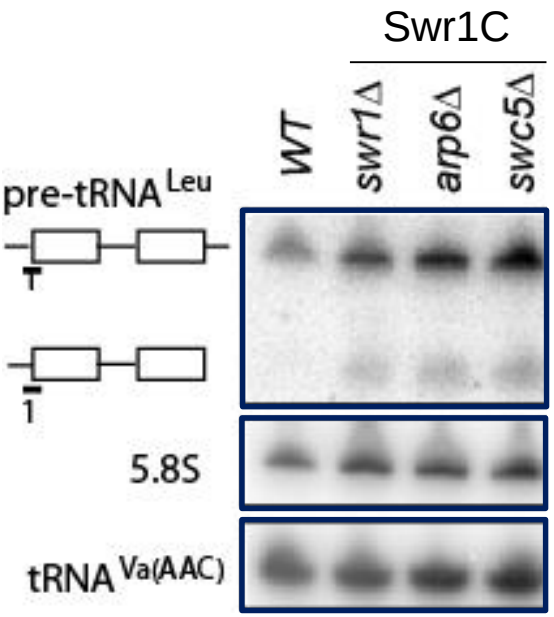
76 double knockouts: *swr1Δ,yΔ*

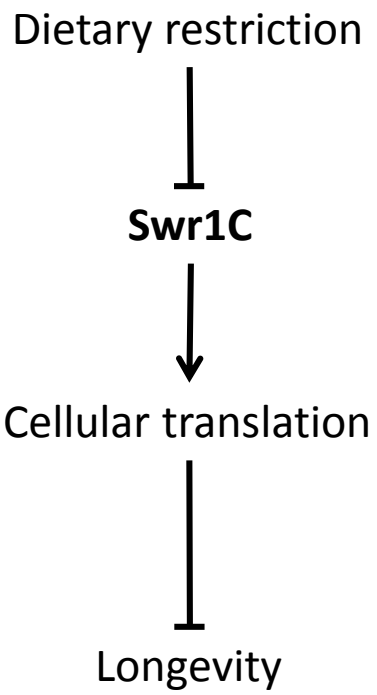


NR-medium

The Swr1C histone-exchange complex is required for pre-rRNA processing and tRNA transcription



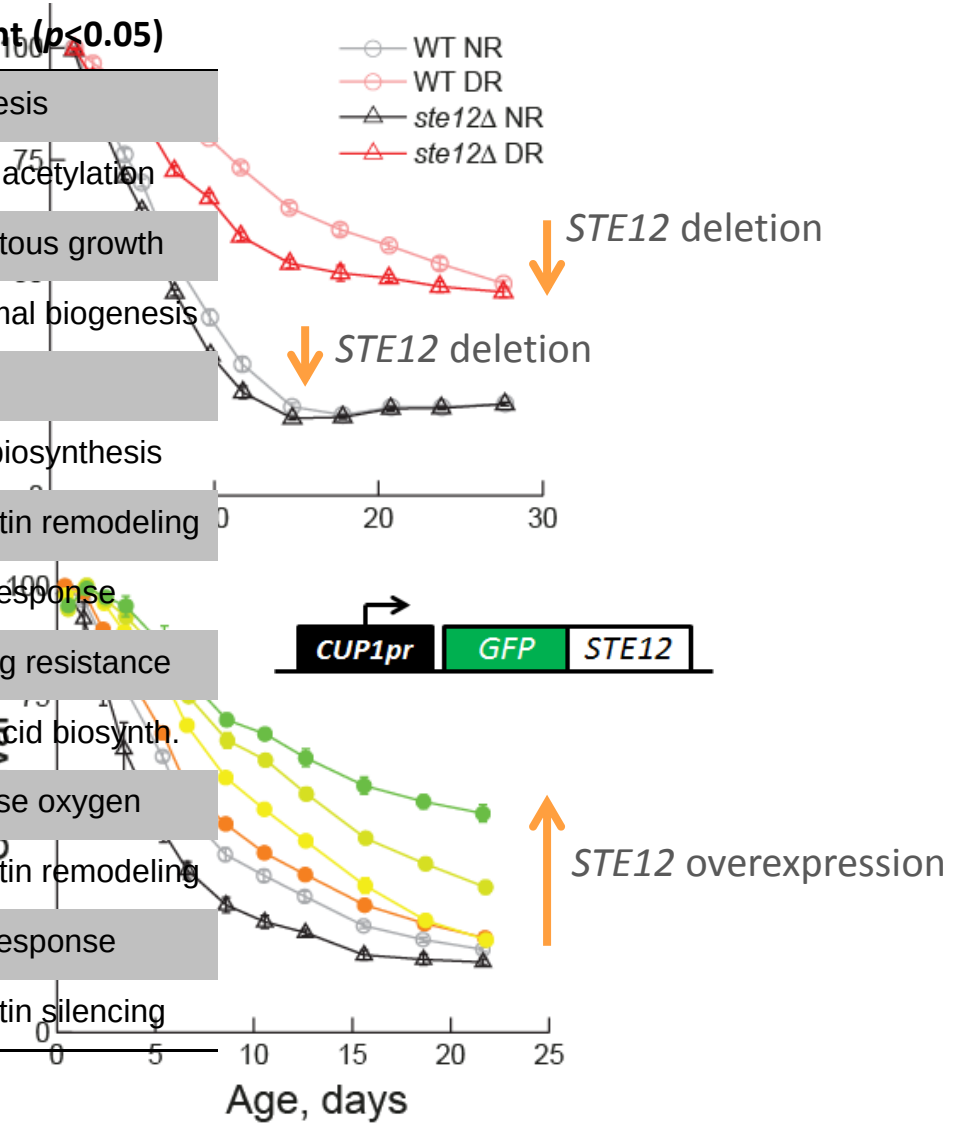




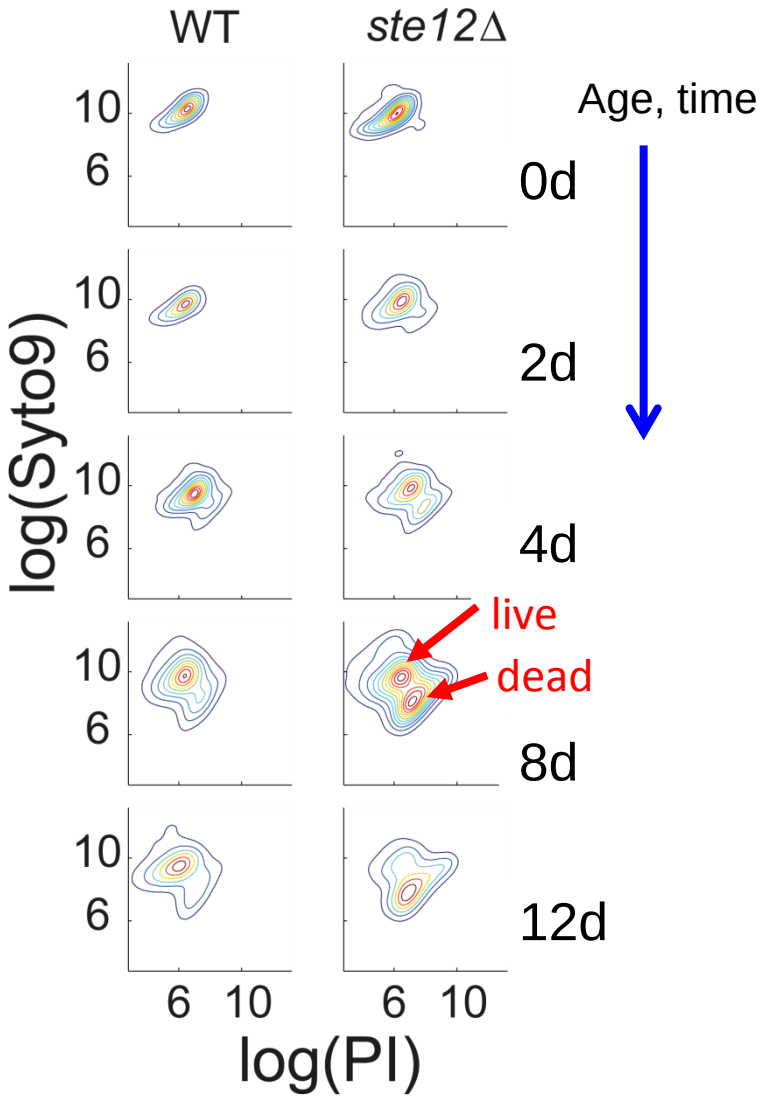
X

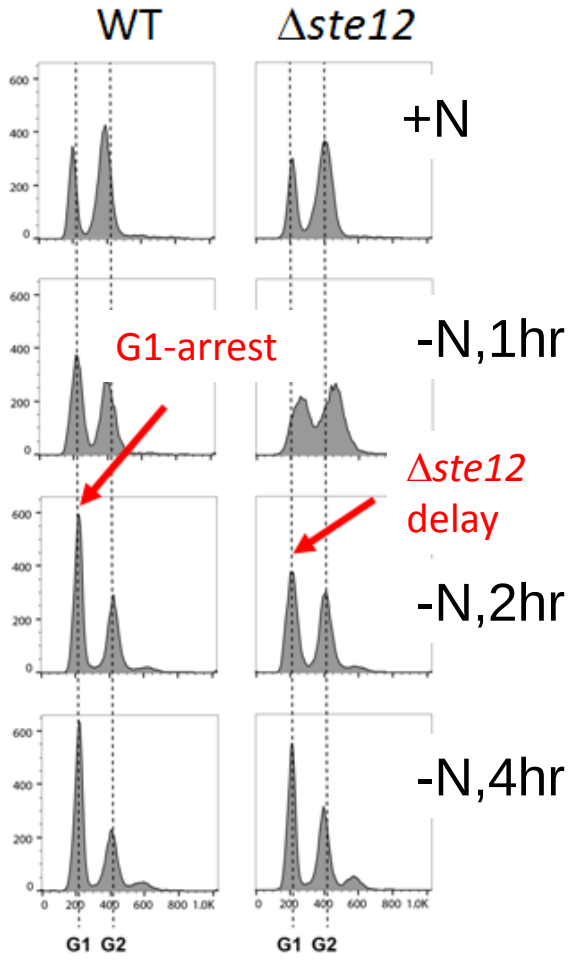
We uncovered a defined set of **transcription factors** that control cellular response to dietary restriction

rnk	TF enrichment (p<0.05)		rnk	TF enrichment (p<0.05)	
1	Ace2	Cytokinesis		Ace2	Cytokinesis
2	Ash1	Histone acetylation	2	Ash1	Histone acetylation
3	Tec1	Filamentous growth		Tec1	Filamentous growth
4	Sfp1	Ribosomal biogenesis	4	Sfp1	Ribosomal biogenesis
5	Ste12	Mating		Ste12	Mating
6	Bas1	Purine biosynthesis	6	Bas1	Purine biosynthesis
7	Snf6	Chromatin remodeling		Snf6	Chromatin remodeling
8	Msn2	Stress response	8	Msn2	Stress response
9	Yrm1	Multidrug resistance		Yrm1	Multidrug resistance
10	Gcn4	Amino acid biosynth.	10	Gcn4	Amino acid biosynth.
11	Ixr1	Response oxygen		Ixr1	Response oxygen
12	Abf1	Chromatin remodeling	12	Abf1	Chromatin remodeling
13	Msn4	Stress response		Msn4	Stress response
14	Rap1	Chromatin silencing	14	Rap1	Chromatin silencing

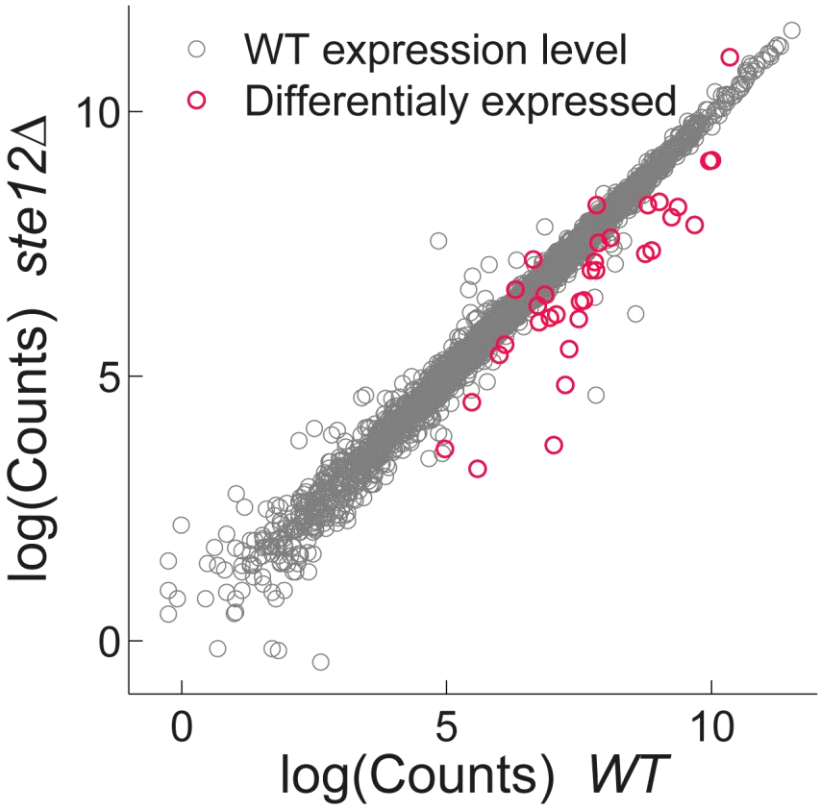


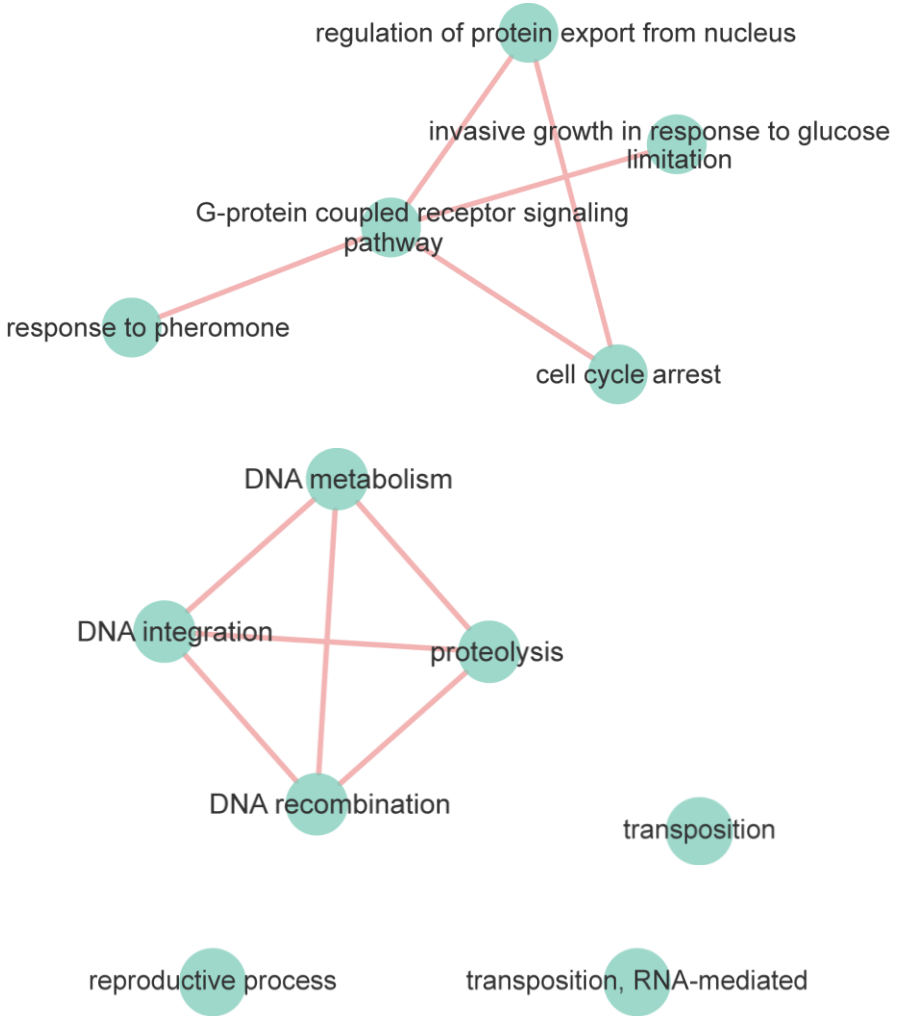
The transcription factor **Ste12** mediates cell-cycle arrest and lifespan extension in response to nutrient limitation



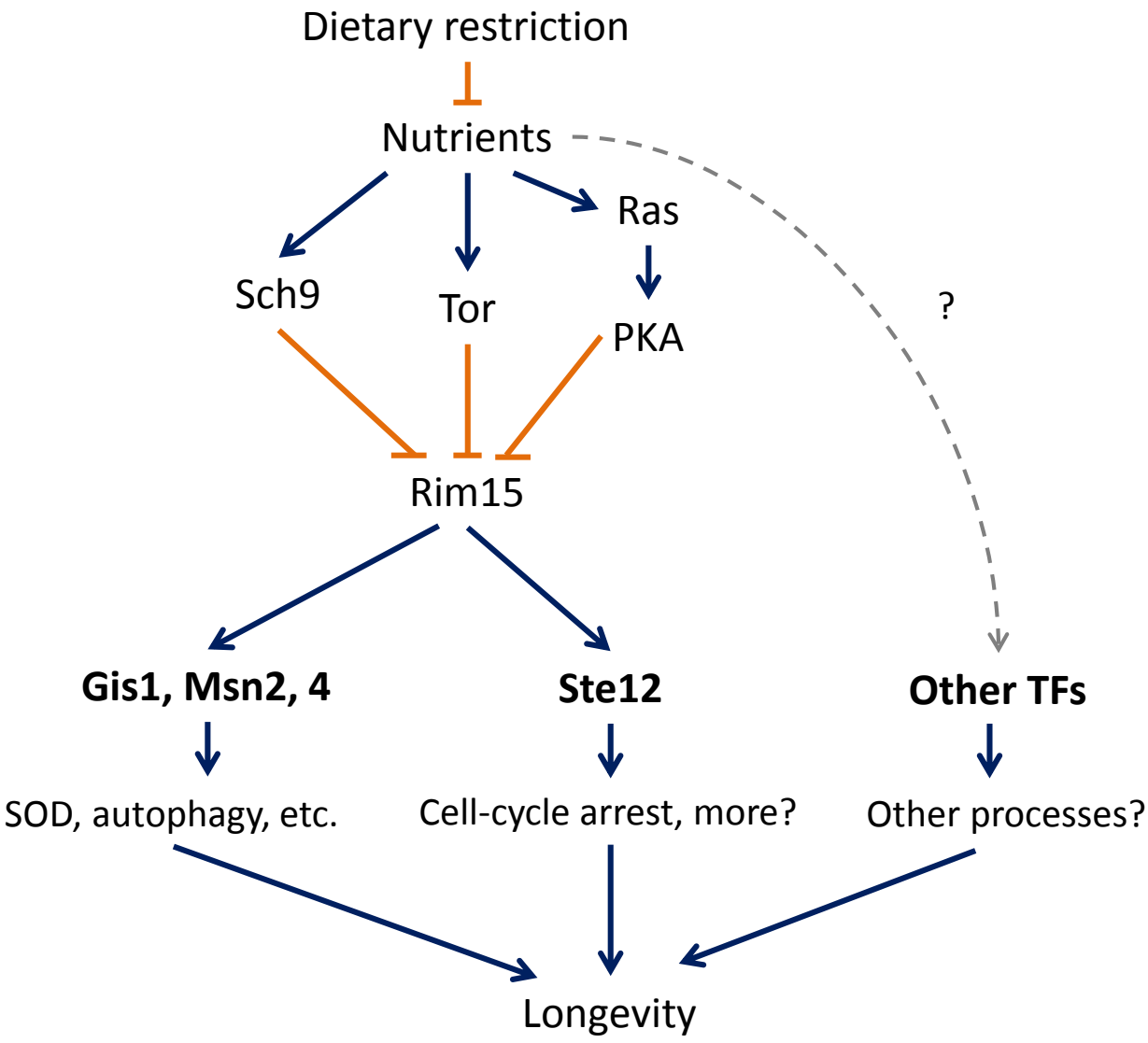


RNAseq-analysis reveals possible **targets** downstream of Ste12



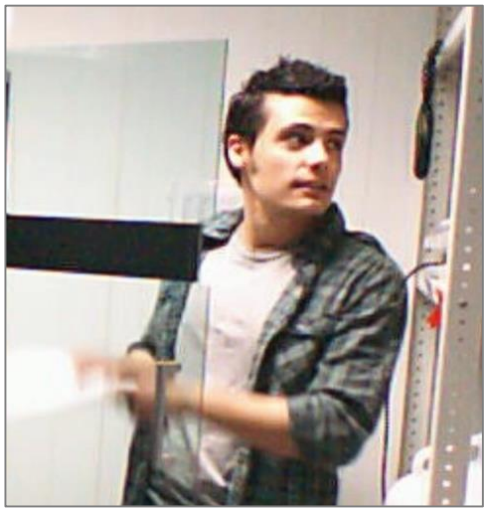


Condition: Dietary restriction


Dietary restriction
Nutrients
Ras
Sch9
Tor
PKA
?
Rim15
Gis1, Msn2, 4
Ste12
Other TFs
SOD, autophagy, etc.
Cell-cycle arrest, more?
Other processes?
Longevity

Erika Garay

Genome-wide lifespan screens



Sergio E. Campos

Dietary-restriction mechanisms

J. Abraham Avelar

Lifespan genetic-interaction networks

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