

# ONE HUNDRED OF CELLS GENERATIONS CONNECT THE RESISTANCE TO DRUGS AND THE REPLICATIVE AGING MECHANISMS



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## Introduction

One of the main reasons why cancer treatments fail is the development of resistance to antineoplastic drugs by cancer cells. This is a very serious problem as it can lead to recurrence of the disease and even death.

Aging itself is the leading risk factor for an array of diseases that increasingly plague the world population. The replicative aging is defined as the number of daughter cells that a progenitor can generate during its life. Due to its characteristics it is used as a biological model for the study of aging in mitotically active tissues.

There are researchs that reveal a relationship between acquired resistance to antineoplastic drugs and aging.

Because of its well-characterized genome, *S. cerevisiae* will continue to serve as a leading model organism for studying pathways relevant to aging and acquired resistance to antineoplastic drugs. Therefore, the identification of genes involved in senescence could have a potential therapeutic utility for the prediction and/or prevention of resistance to antineoplastic drugs.

## Objectives

The aim of this work is to study the relationship between replicative aging and acquired resistance to Cisplatin and Bleomycin in the yeast *Saccharomyces cerevisiae*.

## Material and methods

### Yeast strain and culture medium

The experiments were carried out with the haploid yeast strain *Saccharomyces cerevisiae* WS8105-IC (genotype: MAT $\alpha$ , ade2, arg4-17, trp1-289, ura3-52), with the resistant haploid yeast strain to cisplatin *Saccharomyces cerevisiae* WS8105-IC-R300cisPt and with the resistant haploid yeast strain to bleomycin *Saccharomyces cerevisiae* WS8105-IC-R 0.158 Bleo. Yeast cells were grown in a solid medium of YPD (1 % Bacto-yeast extract, 2 % Bacto-peptone, 2 % dextrose and 2 % Bacto-agar).

### Experimental protocol

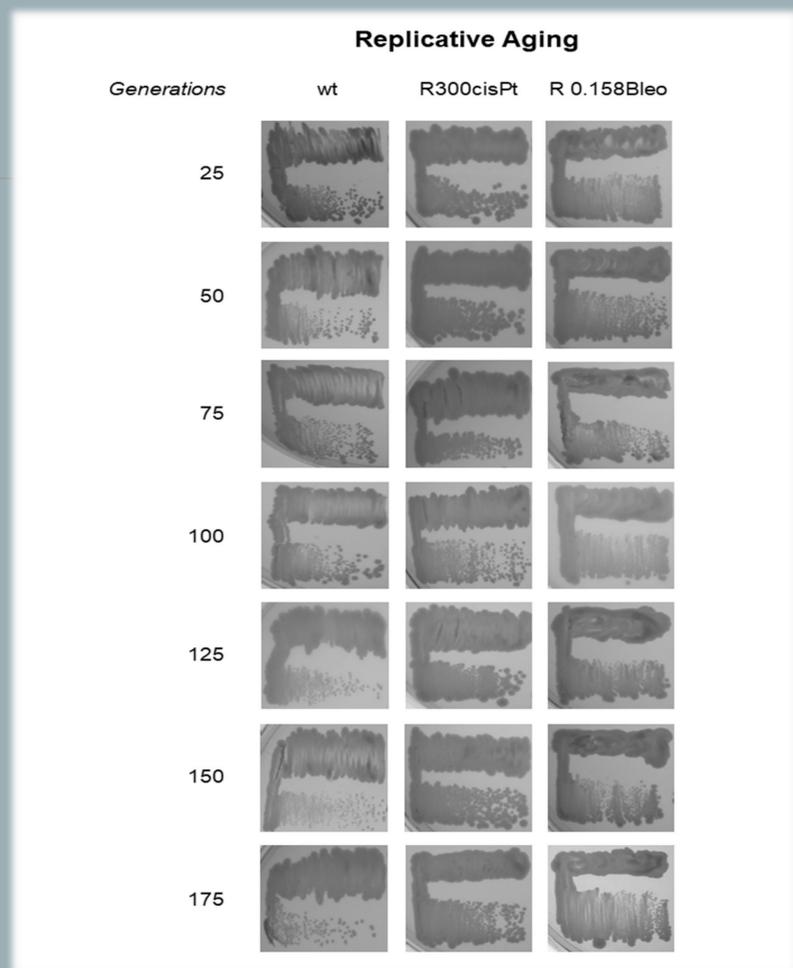
A loop of cells was spreaded following a square pattern onto YPD plates. Then, the samples were incubated during 5 days at 30°C, and next the samples were seeded. The same protocol was carried out 9 times (9 phases). Each phase represents approximately 25 generations; therefore, it was obtained approximately until generation 225.

## Results and Conclusions

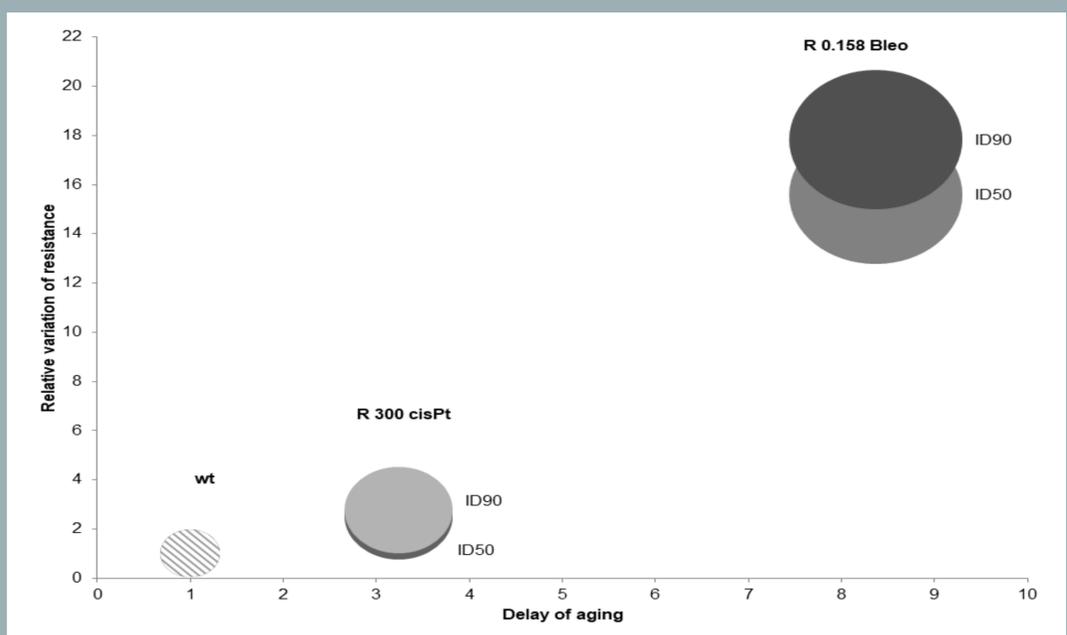
There was a delay of aging in the strain WS8105-IC-R300cisPt (resistant to Cisplatin) and in the strain WS8105-IC-R 0.158 Bleo (resistant to Bleomycin), with respect to the wild type.

The delay in replicative aging started from generation 100, where there were some differences of the strain WS8105-IC-R300cisPt with the wild strain and a marked difference between strain WS8105-IC-R 0.158 Bleo and the wild strain. Due to the analysis is qualitative and purely visual, we can say that the delay is manifestly evident in generation 175.

In conclusion, the strain WS8105-IC-R300cisPt and the strain WS8105-IC-R 0.158 Bleo present an increase in the replicative life cycle, producing a delay in aging after 100 generations. This fact suggests that it is possible that there are common cellular and molecular mechanisms between the acquisition of resistance to these drugs and the delay in replicative aging that could be cumulative into new generations of cells.



Cells generations in replicative aging.  
wt: wild strain (control), WS8105-IC-R300cisPt: resistant to Cisplatin.  
WS8105-IC-R 0.158 Bleo: resistant to Bleomycin.



Correlation between Cisplatin and Bleomycin resistance, and delay in aging