

## Evaluating the role of p38 MAP kinase in the accelerated ageing of WS fibroblasts

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## What is Werner Syndrome? 1- physiology

- Werner syndrome is an autosomal recessive disorder that belongs to a category of diseases called premature ageing disorders
- WS individuals display the premature onset of many age-related phenotypes:
  - *juvenile bilateral cataracts*
  - *tight skin and skin atrophy*
  - *premature hair-greying and hair loss*
  - *symptoms of age-related diseases such as type II diabetes mellitus, osteoporosis, and premature atherosclerosis*
- Age of diagnosis in the late thirties
- Major cause of death is myocardial infarction at a median age of 47
- Widely used a model for some aspects of normal ageing

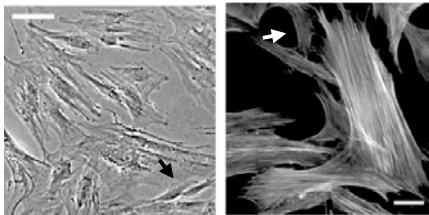


## What is Werner Syndrome? 2- cell biology

- WS fibroblasts have much reduced growth rate
- WS fibroblasts have much reduced replicative capacity
- WS fibroblasts look senescent even when young

*These features may be causal to the accelerated ageing in this disease (Kipling, et al., Science 305, 1426-1431; 2004)*

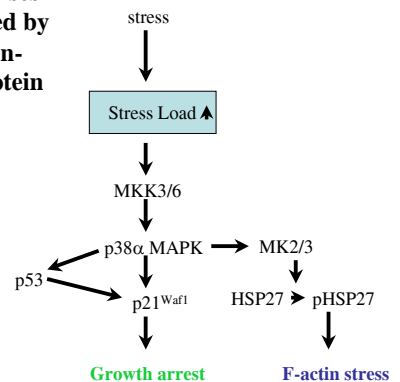
WS fibroblasts resemble cells that have undergone stress-induced premature senescence  
young AG05229 cells



phase contrast x10;

phalloidin x20

Stress responses are transduced by p38 mitogen-activated protein kinase

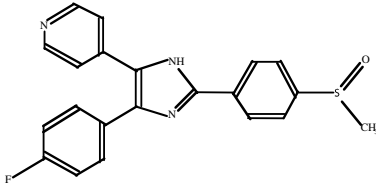


## SB203580 abrogates the p38 stress response

### SB203580

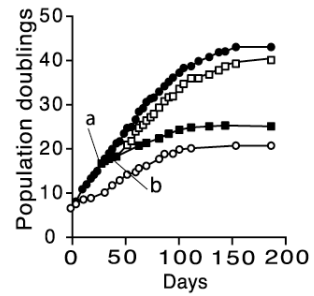
Inhibits the  $\alpha$  and  $\beta$  forms of p38 MAPK

No effect on the  $\gamma$  and  $\delta$  forms

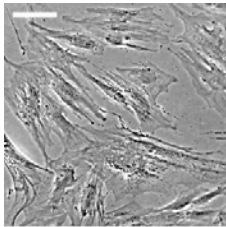


4-[5-(fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-imidazol-4-yl]pyridine

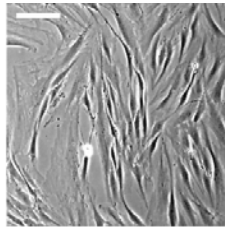
## Effect of SB203580 on WS cell growth (AG05229C cells)



## Effect of SB203580 on cell morphology

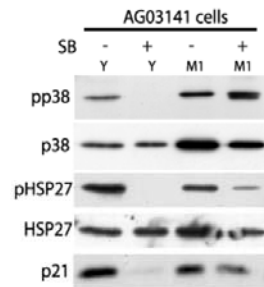


young control  
AG05229 cells



young SB203580 treated  
AG05229 cells

## Immunoblot analysis of p38 activity



## However!?

SB203580 also inhibits other kinases that may affect cellular growth



## Therefore--

- Use a p38 that is resistant to SB203580, express in WS cells and test effects of drug
- Use siRNA knockdown of RIP kinase and test effects of Drug
- Use drugs with selectivities for the other possible targets, e.g., for JNK

•By these means get a clearer understanding of the mechanism of action of SB203580 in WS cells.

## Future--

Once the actual mechanisms of action of SB203580 are elucidated, it is hoped that drugs of this class may be used as therapeutics for WS, *e.g.*, in the Werner mouse model initially.

If stress mechanisms are prevalent to normal ageing, then perhaps p38 therapeutics may be relevant to normal ageing.

## Acknowledgements



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