

# Drugs: Cell Ageing

Therapeutics

Atherosclerosis

Stress

Senescence

## p38 MAPK in rapid Werner syndrome cell ageing

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### The Investigation

#### Objectives

Werner is a progeroid syndrome that has numerous features of accelerated ageing, including premature hair greying, cataracts, skin ageing, and is associated with early onset of atherosclerosis and type II diabetes. WS is widely used as a model for certain aspects of normal ageing [1]. In addition, WS fibroblasts have a much reduced *in vitro* lifespan. The rapid ageing of WS cells is thought to underlie many of the accelerated ageing features of WS individuals. Recent work has shown that a drug (SB203580) that inhibits the stress-associated MAP kinase p38 prevents this accelerated ageing of WS cells [2]. However, the actual kinase target of SB203580 is not clear as it can inhibit other kinases that may be involved in the rapid *in vitro* ageing.

This project will explore whether p38 is the prime target for the action of SB203580.

#### Plan

- (1) We will express an SB203580-resistant form of p38 in WS cells.
- (2) We will target the kinase RIPK2, which is upstream of p38, using siRNA knockdown.
- (3) We will use inhibitors that target the kinases JNK1/2 and CK1.

In each case we will determine the effects on WS cells and see whether SB203580 is still effective at preventing the rapid ageing. By these means we will address whether p38 is the prime target for SB203580 action. This will then pave the way for research to investigate the underlying cause of the stress in WS. In addition, once the prime target is identified then therapeutic possibilities are in mind.

#### Partners

Dr Mark Bagley, School of Chemistry, Cardiff University

#### References

- [1] Kipling, (2004) *Science*, **305** 1425;
- [2] Davis, (2005) *JGA*, **40**, 1386

### Potential Benefits

#### For older people

Individuals with WS show early onset of athero-sclerosis, osteoporosis and type II diabetes. In addition, they have high circulating plasma levels of TNF $\alpha$ . This is suggestive of high inflammatory levels. The p38 MAP kinase plays a pivotal role in inflammatory processes. If, as our data suggests, p38 is involved in the rapid senescence of WS cells, then it is possible that anti-inflammatory drugs such as SB203580 (or derivatives) may form the basis of therapeutics for WS. If inhibition of p38 *in vivo* can reduce the levels of TNF $\alpha$ , these may reduce the probability of developing coronary heart disease and may result in a longer life.

#### For society

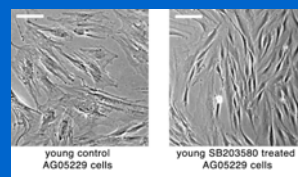
Indeed, as atherosclerosis and other inflammatory diseases are a major public health problem, it is possible that studies into WS may shed some insight into the underlying causes. Thus, therapeutics developed for WS may find use in normal individuals.

#### Individual with WS



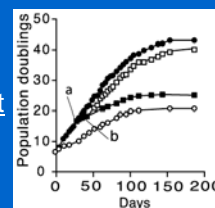
Taking its toll. As a teenager (left) this Japanese American looked normal, but by age 48, the effects of Werner's syndrome were readily apparent. [Image credit: William and Wilkens Publishing Inc.]

#### Stressed cells in WS



#### Correction of cell stress and increase in lifespan using SB203580 treatment

Open circles: control  
Closed circle: SB203580 treated



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