

# Chemical Tools

Werner's Syndrome

Senescence

Synthesis

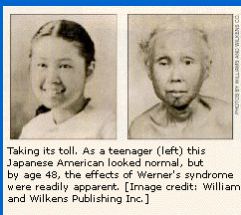
p38 MAPK

## Chemical Tools for Ageing Research

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### The Investigation

**Werner's Syndrome (WS)** is characterized clinically by the premature appearance of features associated with normal ageing and is caused by mutation in a recQ helicase (*wrn*).<sup>1</sup> Symptoms include loss and greying of hair, hoarseness, scleroderma-like skin changes, bilateral ocular cataracts, type 2 diabetes mellitus, hypogonadism, skin ulcers, and osteoporosis in the 30's. Myocardial infarction and cancer are the most common causes of death, typically at an age of around 48 years.<sup>2</sup>



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 Wilkins Publishing Inc.]



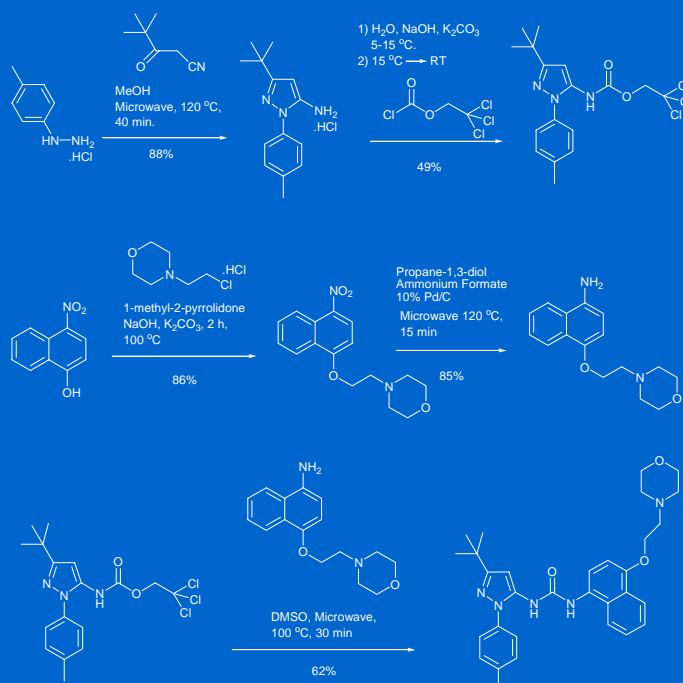
George Martin and a 36 year old WS patient

**Mitogen Activated Protein Kinases (MAPK)** are transferase enzymes which relocate a phosphate group from ATP to another molecule. They are a group of serine/threonine phosphorylating enzymes which regulate the production of cytokines in signal transduction, activated by extracellular stimuli. Specifically p38 MAPK is implicated in transducing the stress signal arising from stalled replication forks, leading to telomere independent senescence. p38 MAPK is activated in response to inflammatory cytokines, excessive production of which are thought to cause inflammatory and stress related diseases. Inhibition of this pathway will hopefully provide treatments for inflammatory diseases but also, it is proposed, could rescue premature senescence in WS cells. From previous research BIRB 796 was chosen as the first inhibitor of study. Inhibition of TNF- $\alpha$  in THP-1 cells ( $EC_{50}$  180nM) is a factor of between 20 and 1000 times more active than many other readily available inhibitors.<sup>3</sup>

### References

- Rodriguez-Lopez, A.M, et al, 2002, *Aging Cell*, 1, 30-9.
- Medical subject heading, MSH2005\_2004\_10\_12, <http://www.diseasedatabase.com/umlsdef.asp?glnquserchoice=14096>.
- Regan, J, et al, *J. Med. Chem.*, 45, 2994-3008.

### Synthesis of BIRB 796



**Effects of BIRB 796 on WS cells.** Preliminary data indicate that the growth rate and cell morphology of WS cells are restored on treatment with BIRB 796. If verified, this supports signal transduction by p38 $\alpha$  MAPK triggering telomere-independent senescence and indicates how this process can be halted in the future.

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