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).1 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.2

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-α in THP-1 cells (EC50 180nM) is a factor of between 20 and 1000 times more active than many other readily available inhibitors.3

References