

Rapid Ageing

Werner's Syndrome

Drug Development

Cell Growth

Cell Signalling

Chemical Tools for Ageing Research

Mark Bagley, Terence Davis, David Kipling, Paola Murziani & Caroline Widdowson

Cardiff University

Werner's Syndrome

Werner's Syndrome (WS) is characterized clinically by the premature appearance of features associated with normal ageing. It is a rare genetic disorder effecting less than one in a million people. Symptoms include loss and greying of hair, hoarseness, wrinkled skin, cataracts, diabetes, hypogonadism, skin ulcers, and osteoporosis in the 30's. Heart attacks and cancer are the most common causes of death, typically at an age of around 48 years.¹ WS cells are used as a model system to study the ageing process and it is how that process can be affected that is the object of this research.



A Puerto Rican family. From left to right: grandmother, mother, individual with Werner syndrome (age ~45), sister, brother with Werner syndrome (age 25), father.

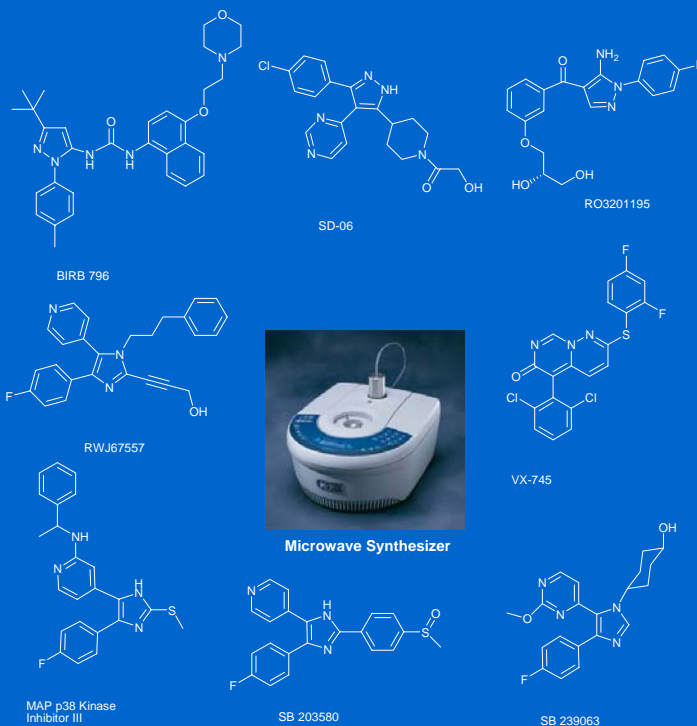
Drug Development for Werner's Syndrome (WS)

The objective of our study is to develop microwave-mediated syntheses of p38 MAPK (Mitogen Activated Protein Kinase) inhibitors. This class of compounds inhibits an enzyme which, upon activation, is proposed to cause rapid ageing in WS cells. A selection of p38 MAPK inhibitors have been investigated, some of which are in human clinical trials for ailments such as rheumatoid arthritis and Crohns disease.² Normal human cells are capable of only a finite number of divisions (50-60 times) after which they stop growing, whereas WS cells only divide an average of 10-15 times. The shape of WS cells is also different, clearly showing features of stress. When testing potential drugs it is the number of cell divisions and morphology (shape) that we look to rescue by administering a p38 MAPK inhibitor.

Synthesis of WS Drugs

Since the study of ageing in human cells takes a protracted period of time, we are developing rapid routes to compounds of interest to facilitate the biological studies. This is only possible using modern synthetic methods, employing microwaves to greatly accelerate the lengthy process of making molecules. A range of different compounds prepared by these means provides complementary data on the biological mechanisms of ageing in WS cells and thus should provide new insights into the ageing process.

Potential Drugs For WS



References

1. Medical subject heading, MSH2005_2004_10_12, <http://www.diseasedatabase.com/umlsdef.asp?glnuserchoice=14096>
2. Regan, J, et al, *J. Med. Chem*, **45**, 2994-3008.

Contact Details



Principal Investigator
Dr Mark Bagley
bagleymc@Cardiff.ac.uk
School of Chemistry, Main Building
Cardiff University, Park Place
Cardiff, CF10 3AT



Researchers
Caroline Widdowson, Paola Murziani
cazwiddowson@hotmail.co.uk
paolamurziani@tiscali.it
+44 (0)29 2087 4029