blastoma that had metastasised to the bone marrow. Figure 4 shows structurally distinct forms. In tissue culture, cells grow in the S-form, which is partially differentiated and characterised by the irregular shapes of the cells. These cells undergo two responses to stress: full differentiation or cell death. Full differentiation is observed by the more 'dendritic' appearance of the cells, which occurs 1–3 hours after the stress. Subsequently cells either dedifferentiate back to the S phase – if the stress can be overcome – or die.

Concluding Remarks

Ruthenium drugs are particularly important in the clinic due to their low toxicity. This is in part due to the ability of ruthenium to mimic the binding of iron to biomolecules, exploiting the mechanisms that the body has evolved for non-toxic transport of iron. In addition, the redox potential between the different accessible oxidation states occupied by ruthenium enables the body to catalyse oxidation and reduction reactions, depending on the physiological environment. As demonstrated for cancer tissues, but also true in other diseased states, the biochemical changes that accompany disease alter the physiological environment, enabling ruthenium compounds to be selectively activated in diseased tissues. These two features combine to give ruthenium drugs a remarkably low toxicity compared to other platinum group metal compounds and therefore make ruthenium compounds promising in the clinic.

Acknowledgement

Paul J Dyson would like to thank the Royal Society for a University Research Fellowship.

Bibliography

M. J. Clarke, F. Zhu and D. R. Frasca, 'Non-platinum chemotherapeutic metallopharmaceuticals', *Chem. Rev.*, 1999, **99**, 2511–2534

Z. Guo and P. J. Sadler, 'Medicinal inorganic chemistry', *Adv. Inorg. Chem.*, 1999, **49**, 183–306

G. Sava, E. Alessio, A. Bergamo and G. Mestroni, 'Sulfoxide ruthenium complexes: non-toxic tools for the selective treatment of solid tumor metastases', in "Metallopharmaceuticals I, DNA Interactions", eds. M. J. Clarke and P. J. Sadler, Springer-Verlag, Berlin, 1999, pp. 143–169

A. Eastman, 'The mechanism of action of cisplatin: from adducts to apoptosis', in "Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug", ed. B. Lippert, Wiley-VCH, Weinheim, 1999, pp. 111–134

M. J. Abrams and B. A. Murrer, *Science*, 1993, **261**, 725–730 (A general reference on metals in medicine)

S. P. Fricker, 'Nitrogen monoxide-related disease and nitrogen monoxide scavengers as potential drugs', in "Metal Ions in Biological Systems", Volume 36, eds. A. Siegel and H. Siegel, Marcel Dekker Inc., New York, 1999, pp. 665–721 (A review on metal compounds and nitric oxide focusing on ruthenium compounds)

M. J. Abrams, 'Ruthenium Phthalocyanines', *Platinum Metals Rev.*, 1995, **39**, (1), 14–18

S. P. Fricker, 'Ruthenium, Nitric Oxide and Disease', *Platinum Metals Rev.*, 1995, **39**, (4), 150–159

The Authors

Paul Dyson is a Royal Society Fellow in inorganic chemistry at the University of York. His interests are in functional ligand design for catalysis and medicine.

Claire Allardyce is a Research Fellow at the University of York. Her main interests are in biological structure in relation to toxicology and drug design.

Thiazepinones Synthesis with Rhodium

Thiazepinones are pharmaceuticals with potential use in the treatment of heart and inflammatory diseases. The 7-membered heterocycles have been prepared in multistep syntheses in which chirality is introduced before or during a transformation.

Researchers at the University of Ottawa, Canada, now report the synthesis of thiazepinones using cyclohydrocarbonylative ring expansion of acetylenic thiazoles in the presence of CO and H_2, via the zwitterionic rhodium complex catalyst (η^6-$C_6H_5BPh_3$)$^-$Rh$^+$(1,5-COD) with added triphenyl phosphite (B. G. Van den Hoven and H. Alper, *J. Am. Chem. Soc.*, 2001, **123**, (6), 1017–1022).

The transformation of the simple and functionalised 5-membered acetylenic thiazoles with CO and H_2 to 7-membered 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones occurred in 61 to 90 per cent yields with good chemo- and regioselectivities, at 70–110°C, after 18 to 36 hours. A model substrate of 2-hex-1-ynylthiazole was used to optimise the cyclohydrocarbonylation and ring expansion of 2-acetylenic thiazoles. The acetylenic unit can have various substituents in positions 4 and 5 of the thiazole ring as well as alkyl-, ether-, ester-, vinyl-, and aryl-substituted alkynes at position 2. The process is general and may be pharmaceutically interesting.