

EDITORIAL

Why Should we Fund your Grant on Multidrug Resistance this Time?

Imagine you have cancer in the era before chemotherapy. The surgeons would do their best to remove the cancer, but the odds were 2 to 1 against you surviving five years. No wonder, when chemotherapy was introduced, there was an overshoot in the optimism of its potential. It provided a glimmer of hope for patients where before there was little hope, it gave physicians something to do post-surgery and its promising potential was used to enhance research grant applications. Although chemotherapy has quietly delivered improvements over the years to give a present cure rate of around 60%, the early expectations were not fulfilled and the optimism was replaced with more pessimistic views that the development of resistance to chemotherapy was somehow an inevitability of the treatment.

In 1976 Victor Ling discovered P-glycoprotein, an ATP-dependent drug efflux pump capable of transporting a wide variety of lipophilic, natural product drugs out of cancer cells. This potentially explained how resistant cancer cells were protecting themselves against chemotherapy. As with the introduction of chemotherapy, there was increased optimism that the effects of P-glycoprotein could be neutralised. Now that there was a molecular entity to blame for resistance, there was a feeding frenzy at the cancer research granting bodies as groups presented their molecular and pharmacological strategies for inhibiting P-glycoprotein. Again, this optimism was not sustained as it became clear that there were many more transporters capable of decreasing drug accumulation and there were

other important mechanisms of drug resistance involving increased DNA repair, glutathione-based drug detoxification and inactivation of apoptosis.

So where is the next wave of optimism going to come from? It will come from a better understanding of the mechanics of these resistance mechanisms and how cells induce and control these mechanisms as part of the cellular stress response. Already there are promising signs appearing in our understanding.

This Showcase on Research will bring you up to date with how resistant cancer cells manipulate their tubulin to lessen the effects of tubulin-targeting drugs (Pasquier and Kavallaris), with the involvement of MRP1/ABCC1 in neuroblastoma (Munoz *et al.*), with the diversity of cellular responses to cisplatin treatment (Stordal and Davey), and with the impact of breast cancer resistance protein/ABCG2 on the efficacy and pharmacodynamics of some drugs (Allen).

The early attempts to inhibit transporters did not deliver on the promises made in the early research grants, but this is changing. There is evidence from our group that the transporter-rich blood brain barrier can be manipulated with agents such as thalidomide to specifically increase cisplatin delivery to brain tumours without any increase in the normal tissues (Murphy S. *et al.*, *J. Neurooncol.* in press). Although we have little understanding of the mechanism responsible, it does show that the holy grail of a tumour-specific increase in drug exposure is possible, as discussed in this Showcase on Research.

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Cover Illustration

Acute lymphoblastic leukaemia cells during metaphase.

Kinetochore microtubules (α -tubulin, red) segregate and separate chromosomes (DAPI, blue) during cell division. Epifluorescence microscopy was performed using an Axioplan 2 microscope and 63x objective (Zeiss, Oberkochen, Germany), and images were captured using a Sensicam Charged Coupled Device (CCD) camera (PCO Imaging, Kelheim, Bavaria, Germany).

Image courtesy of Maria Kavallaris.

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