

How new drug technologies might overcome toxicity from chemotherapy

A new approach to cytotoxic drug delivery, which addresses problems of tumour resistance and drug toxicity, is the subject of the latest article in our new drug technologies series. **Jenny Bryan** reports

Tumour resistance and drug toxicity are two of the greatest challenges facing today's cancer specialists. But a novel approach to cytotoxic drug delivery — currently undergoing phase I clinical trials — addresses both problems in a single prodrug design. Banoxantrone (AQ4N) is the first hypoxic cell-activated anti-tumour therapy that uses the low oxygen conditions of many cancer cells for conversion to its active, cytotoxic form.

Under joint development by KuDOS Pharmaceuticals in the UK and San Francisco-based Novacea in the US, AQ4N was discovered by Laurence Patterson, newly appointed director of the Institute of Cancer Therapeutics in Bradford, and formerly head of pharmaceutical and biological chemistry at the School of Pharmacy, University of London.

Professor Patterson explains that the idea of using prodrugs to target cancer cells has not previously been popular, partly because of concerns about patient variability in the way they metabolise prodrugs to active compounds. But the lack of toxicity seen in phase I studies of banoxantrone lends fresh support.

"It addresses the twin evils of the systemic toxicity that you get from cytotoxic drugs that can't distinguish between tumour and healthy cells, and the resistance which so many cancers develop to standard treatments," he says.

The conventional approach to resistance is to look for ways to down-regulate the mechanisms that enable cancer cells to lose their responsiveness to cytotoxic agents. But the hypoxia approach uses the natural conditions which exist in parts of many tumours.¹

"We need to look at tumours as systems rather than as collections of cells and a tumour is like an organ that is out of control. It can develop a well-defined architecture which is supported by its own blood vessels. However, it's a poorly defined, leaky blood supply that doesn't supply the whole tumour with enough oxygen, so some areas remain hypoxic," says Professor Patterson.

With too little oxygen, some hypoxic cancer cells will die, but the survivors become a hard-core population that is likely to be resistant both to cytotoxic drugs and radiotherapy. However, the hypoxic conditions work in favour of banoxantrone, and hopefully future hypoxic cell-activated cytotoxic agents.

Banoxantrone is preferentially metabolised to its active form by the cytochrome P450 system of hypoxic cells, so it is hoped that it will be particularly effective in drug-resistant solid tumours. Initial trials have focused on treatment-resistant oesophageal tumours, and further studies will test the drug alone, and in combination with other cytotoxic agents

or radiotherapy, in head and neck, breast and lung tumours. A further refinement of the approach has been to combine banoxantrone with P450 gene therapy, in order to enhance P450 levels, and thus further improve the activation of banoxantrone in hypoxic tumour cells.²

Using tumour hypoxia in the development of novel anti-cancer drugs will be an important aspect of the research programme which Professor Patterson is planning for the Institute of Cancer Therapeutics — scheduled to move into state-of-the-art premises at Bradford University in 2006.

"We will be pursuing the next generation of agents, but also looking at other ways of dealing with resistance, including the ultimate form of resistance — metastasis," he explains.

High on the agenda will be research into how cancer cells detach from primary tumours en route to forming metastases. At least one factor has already been identified as a target for anti-metastatic agents designed to prevent cancer cells breaking away from primary tumours.

Professor Patterson predicts that such agents will be administered after cancer surgery to help stabilise and control any primary tumour that may have been left behind, thus enabling patients to live with their cancer for prolonged periods. "One approach will be to use non-toxic agents for long-term treatment to prevent [the breaking away] of cancer cells from primary tumours to form metastases, and the second, more conventional approach will be to try to destroy both primary and secondary tumours," he says.

The advantage of moving to Bradford to develop such research, explains Professor Patterson, is the opportunity to bring the full cancer medicines discovery process together

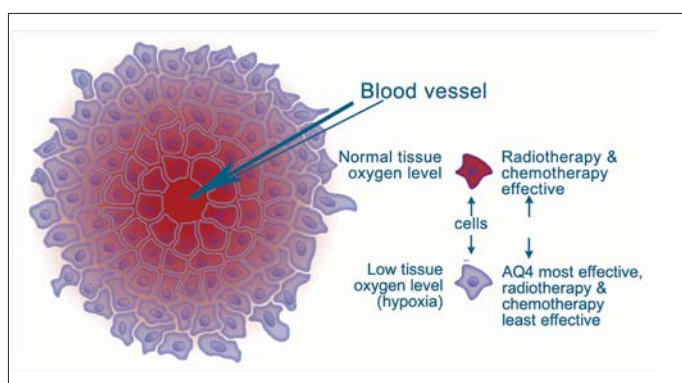


Illustration of hypoxia, which provides the conditions for banoxantrone to work

— from concept to clinic. The new institute will have funding from Cancer Research UK, Yorkshire Cancer Research and, through its collaborative partnership with Leeds, the government-funded National Translational Cancer Research Network (NTRAC).

Leeds-Bradford is one of 14 centres with NTRAC status and funding to integrate scientific and clinical trial research. It is also one of a handful of centres with the capacity to take new molecules from design to phase I clinical trials. Once phase I trials have shown that a new anti-cancer compound has promise, researchers such as those at Leeds-Bradford will need to find commercial partners for phase II and III trials. But does Professor Patterson now see himself in competition with the pharmaceutical industry in which he once worked?

"Cancer is such a huge problem that there is a role for everyone," he says diplomatically. "Ten years ago, there was a clear distinction between academia and commerce, but the border is now much more blurred. Academia is being actively encouraged to contribute to Great Britain Plc, and it is the academic's job to progress more radical ideas and approaches to cancer treatment than may be possible within a wholly commercial environment."

References

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2. McErlane V, Yakkundi A, McCarthy HO, Hughes CM, Patterson LH, Hirst DG et al. A cytochrome P450 2B6 mediated gene therapy strategy to enhance the effects of radiation or cyclophosphamide when combined with the bioreductive drug AQ4N. *Journal of Gene Medicine*. 2005;(February 11): [Epub ahead of print]. Available at: www.ncbi.nlm.nih.gov (accessed 17 March 2005).

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