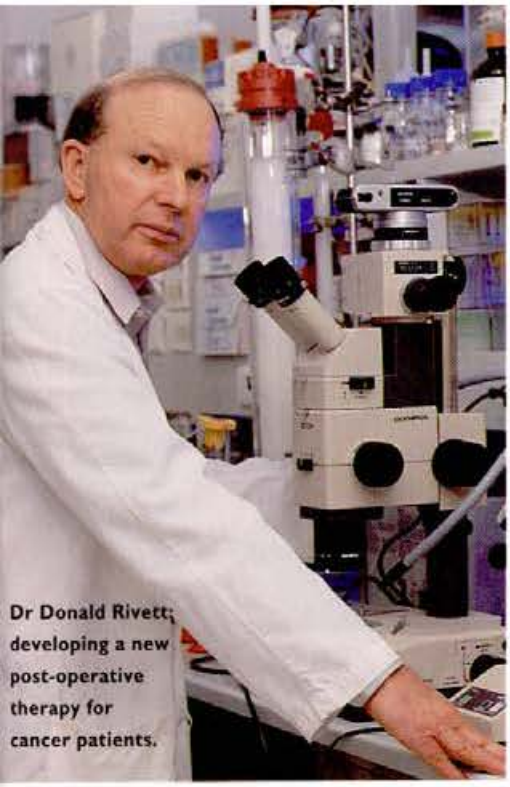
A sting in the tail for cancerous cells



Dr Donald Rivett; developing a new post-operative therapy for cancer patients.

A honeybee's sting means pain for its victim and death for the bee. But Dr Donald Rivett hopes a component of bee venom, melittin, may one day alleviate suffering and prolong the lives of many cancer patients.

Rivett is a protein chemist with CSIRO's Division of Biomolecular Engineering at Melbourne. In 1986 he began a joint research project with Sydney University immunologist Professor Bob Raison, to explore melittin's potential as a 'magic bullet' to eliminate residual cancerous cells after patients have undergone surgery to remove solid tumors. The cell-killing toxin would be delivered to cancerous cells by linking it to monoclonal antibodies (MABs), selected to 'zero in' on specific molecular targets on tumor cells.

Rivett says the 'magic bullet' idea is not new. The great immunologist Paul Ehrlich senior conceived the basic idea early this century, but it has only recently become technologically feasible, thanks to a recombinant DNA technique pioneered by the division's Dr Peter Hudson. The technique enables human monoclonal antibodies to be produced in specialised viruses called bacteriophages which infect and re-program the protein-synthesis machinery of bacteria. The system can actually deliver a hybrid antibody-melittin molecule in one seamless operation.

After their initial collaboration, Rivett and Raison took divergent paths for several years. Raison moved to the University of Technology Sydney, where he worked on conjugation, the business of linking whole melittin molecules to a selected monoclonal antibody. In Melbourne, Rivett took the melittin protein apart to see what made it tick. Without compromising melittin's cell-killing action, he excised a small peptide sequence that poses a hazard to certain individuals who are allergic to bee stings.

Rivett says because of its unusual cell-killing action, melittin is safer than the better-known toxin ricin, derived from the castor oil plant. Ricin is nature's most potent toxin; a single molecule of the ricin A-chain will kill a cell by entering its cytoplasm and switching off its protein-synthesis machinery. But ricin's hypertoxicity is a liability due to the danger of it entering the body's healthy cells.

Melittin does not actually enter the cell; it uses its water-repellent tail to anchor itself in the cell's lipid membrane, where its coiled shape forms a molecular pipe through which electrolytes leak from the cell, causing the cell to collapse and die.

Rivett sees melittin-MABs being used to mop up cancerous cells missed by surgery. The technique is unlikely to become a primary therapy, because the magic bullets cannot reach cancerous cells deep inside the tumor mass. But in its mop-up role, melittin should be much gentler on patients than conventional post-operative chemotherapy with methotrexate or adriamycin. Both these compounds work by jamming the cell-division machinery in fast-dividing cancer cells, but this broad-spectrum action causes collateral damage in healthy, rapidly dividing cells, including immune-system cells and cells that make hair and nails.

Because melittin-MABs would be specifically targeted to cancerous cells, there would be no hair or nail loss, or nausea typically experienced with conventional chemotherapy.

'We hope to conduct the first trials on prostate cancer, because researchers have already identified a target called prostate-specific antigen (PSA), which is abundant in prostate cells but rare in other tissues,' Rivett says. 'But we hold great hopes that a similar approach will be applicable to a wide range of tumors, provided researchers can identify tumor-specific antigens.'

As an enzyme, PSA is doubly attractive as a target for melittin. Rivett has found a way of 'tuning' melittin's toxicity, by packaging the molecule in such a way that it would have to be cleaved by an enzyme to release its full cell-killing potential. By designing a molecule that would depend on the PSA enzyme to activate it, Rivett says it should be possible to design an even safer melittin magic bullet that could not fire accidentally in transit.

'It's still very experimental, but we've already shown that Bob Raison's whole-melittin conjugated antibodies work very well on cultured tumor cells in vitro,' Rivett says. 'After wider cell-culture experiments, we would begin trials in laboratory animals. If all goes well and we attract financial support for our research, we would hope to begin the first clinical trials in humans in about five years.'

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environment that supports apogeotropic root growth. Preliminary examinations suggest that the relationship between apogeotropic roots and papery-barked stems is robust and probably exists in a range of north Queensland forests beyond the present study site.

A knowledge of key ecological characteristics of particular rainforests is essential to their management and conservation. The protection of surface root mats, for example, is a dominant theme in the management of some Amazonian forests on nutrient-poor soils. This research was undertaken as part of the Cooperative Research Centre for Tropical Rainforest Ecology and Management program.

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