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Marsupials as models for research

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Marsupials are worth studying for their intrinsic value alone. They are one of the three major extant mammal types, Prototheria (monotremes), Metatheria (marsupials) and Eutheria, and have provided important information about the evolution of mammals. They represent the major mammalian group on the Australian continent, and their study makes an important contribution to our natural heritage. Such studies are necessary in order to stem the further loss of marsupial diversity due to extinction of species. In addition, the study of marsupial species has provided new insights into old problems, because of their value as models to study a variety of totally different fields.

The study of marsupials can be seen as an example of the importance of basic research. Studies of marsupials are usually undertaken because scientists are interested in some intrinsic aspect of marsupial biology, or in comparative biology. From these studies in basic biology, powerful tools to examine other fields, or to apply to specific problems, have become available. These applications were not always obvious or apparent initially, and were not the reason for the original research.

In this special issue of the *Australian Journal of Zoology*, some of these increasingly valuable models are described, and their potential value to study a variety of problems is explored. These papers arose from a symposium on 'Marsupials as Models for Research', sponsored by the Australian Mammal Society. The symposium was held at the Ninth International Mammalogical Congress in Sapporo, Japan, in August 2005.

Because marsupials have two uteri, each with its own cervix, it is possible in monovular species, such as the tammar wallaby, *Macropus eugenii*, to study the effect of the conceptus or the placenta independent of any systemic effect, including the hormones influencing pregnancy or parturition. Geoff Shaw and Marilyn Renfree show in this issue how this model can be used to demonstrate foetal control of the onset of labour (Shaw and Renfree 2006).

Marsupials have proved to be excellent models for the study of sex determination and differentiation of the reproductive system. The success of the marsupial in this respect is because the altricial young exhibit little or no development of the reproductive system at birth, so that development of the reproductive system can be studied in the pouch young, rather than by trying to determine what happens when the conceptuses are implanted in the uterus, as in the mouse. The Renfree and Shaw group has skilfully exploited this in the tammar wallaby, and provided further experimental advantages by developing techniques for gonad sex reversal and female reproductive tract sex reversal in the neonates (Renfree *et al*. 2006). Using marsupials, the development of the scrotum, mammary glands, pouch and *processus vaginalis* are shown to be sexually dimorphic before the testis differentiates, and hence are independent of testicular hormones. These studies have been extended into the molecular level.

Studies on life history strategies of *Antechinus* showed that animals in this genus die from stress-related disorders at the end of the breeding season when they are ~11 months old, during the male die-off in the field. Some males kept in captivity survive the die-off but rapidly become senile. Analysis of this senility has shown that the males exhibit characteristics reminiscent of Alzheimer's disease, including β-amyloid plaques and hippocampal alterations. No other animal naturally shows these neuropathologies, and Bronwyn McAllan has identified *Antechinus* as an excellent model to study some of the degenerative diseases of aging (McAllan 2006). Studies on life history strategies and the ability to enter torpor of another dasyurid marsupial, the stripe-faced dunnart, *Sminthopsis macroura*, demonstrated the interrelationship between aging, energy intake and obesity, making this marsupial a suitable animal model for examining age-related obesity in humans.

Monodelphis domestica, the 'laboratory opossum', has become a widely used model for the study of the marsupial genome at least in part because it is such an excellent laboratory animal and breeds throughout the year. Paul Samollow has shown that the extensive genomic resources available for this marsupial has placed it at the forefront of animals being used as models to look at evolution of the mammalian genome, genomic imprinting and X-chromosome inactivation (Samollow 2006). Some genetic and chromosomal studies of marsupial models have hugely benefited from the small number of chromosomes and the small size of some chromosomes, especially in the stripe-faced dunnart. In addition, *M. domestica* has become the model for the study of melanoma because it is the only animal, apart from

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humans, in which ultraviolet radiation acts as a complete carcinogen to induce malignant melanoma. It is also used as a model to examine neural regeneration, capitalising on the relatively undifferentiated state of the nervous system at birth and to examine the genetic regulation of plasma lipoprotein levels.

Because the dasyurid marsupial conceptus is transparent, cell lineages can be readily traced without the use of markers, and the conceptus remains relatively small and can be readily examined *in vitro*, dasyurids, especially the stripe-faced dunnart, provide excellent models for the study of lineage allocation and early axis formation. These advantages in the dunnart are compounded by its availability in a laboratory colony of 21 years standing and from which embryos of known age can be obtained. Knowledge from these studies in the basic biology of one marsupial has recently been used in an applied study by Lynne Selwood and Shuliang Cui to obtain potential targets for immunocontraception in the common brushtail possum, *Trichosurus vulpecula*, a major agricultural and ecological pest in New Zealand (Selwood and Cui 2006). Two features of marsupial development have been further analysed to provide molecules that will be marsupial specific and hence will not affect other non-target animals in New Zealand. The features that have been thus examined are the shell coat, which is essential for normal development of possum conceptuses, and the molecules associated with the polarised zygote, an essential characteristic of early cell lineage allocation.

In mammals, complex physiological cross-talk between mother and embryo is essential for the establishment of a successful pregnancy, and is achieved mostly by signalling molecules exchanged between mother and conceptus. Maternal recognition of pregnancy is well studied in eutherian mammals, in which gestation is prolonged, and early pregnancy factor (EPF) is one of the first signals produced by the mother. Yolanda Cruz and her colleagues outline the discovery of EPF in marsupials, in which gestation is relatively brief (Cruz *et al.* 2006). This discovery extends the growing inventory of paracrine factors known to be involved in maternal recognition of pregnancy. More importantly, as EPF is found in both Australian and New World marsupials and is pregnancy specific, it indicates that marsupials and eutherians evolved from a viviparous common ancestor in which maternal recognition of pregnancy was mediated by EPF.

The value of marsupials as models is not confined to laboratory studies. Graeme Coulson and his colleagues have identified characteristics of kangaroos that offer insights into an intractable problem in behavioural ecology (Coulson *et al.* 2006). Sexual segregation is well known amongst eutherians, particularly the ungulates. Many hypotheses have been put forward to explain the evolution of this behaviour in ungulates, but the two key explanatory variables, body size and sex, are intrinsically confounded. Coulson and colleagues studied western grey kangaroos, *Macropus fuliginosus*, as ecological analogues of ungulates. This species showed segregation in social, habitat and dietary dimensions but, unlike ungulates, displayed a spectrum of adult body sizes in its heteromorphic population. The independent influences of body size and sex on segregation could then be determined.

This collection of papers illustrates several areas in which marsupials have proved to be valuable models for research. Other areas of basic and applied research have also been enhanced by marsupials. In recent years, marsupials have given new impetus to studies as diverse as surrogacy techniques in assisted reproduction of endangered species, and the causation of global mammal extinctions in the Late Quaternary. We are confident that marsupials will demonstrate their value as models for research in many more fields in the future.

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