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THE ARA-C PRETREATED MOUSE AS A HOST FOR HUMAN TUMOUR XENOGRAFTS

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MICE thymectomized at 3–4 weeks of age and irradiated with 9 Gy can be protected against death by treatment 48 h before irradiation with 200 mg/kg i.p. cytosine arabinoside (Ara-C). As xenograft hosts, Ara-C mice have some advantages over other hosts. They do not require time-consuming bone marrow (BM) reconstitution to prevent death after irradiation; they are less expensive (half the cost) and more robust than nude mice, and they can be conventionally housed.

Cell dilution experiments with a pancreatic xenograft show that fewer tumour cells are needed to produce takes in Ara-C mice than in nudes when hosts were implanted 1 day after irradiation (Steel *et al.*, 1978, *Br. J. Cancer*, **37**, 224). The disadvantage of immune-deprived mice compared with nudes is their returning immunity. Using cells from a passaged human pancreatic tumour (1×10^5 cells/site i.m.) and pieces from a passaged human oat cell carcinoma (2×2 mm s.c.), it was shown that immune competence begins to return in a proportion of mice 3–5 weeks weeks after irradiation. However, this proportion does not rise above 40–60%, even after 6 months. The pattern of returning immunity was similar for male and female hosts. The variability of hosts seen 3–5 weeks after deprivation should not produce many artefacts when *in vitro* assays are used, but tumour growth may be affected, either in the more slowly-growing tumours implanted direct from the clinic or in growth delay studies, or when investigating metastasis.

Hosts which accepted xenografts at late times after deprivation appeared to be as suitable as those implanted early after deprivation. However, hosts which did not accept xenografts initially, never accepted the same xenograft line even if re-deprived and implanted immediately. A large study with human bronchial carcinoma xenografts showed the Ara-C mouse to be a very favourable xenograft host for growing tumours directly from the patient even when the tumours had a lag period of 11–20 weeks before growth could be measured. Various histological types of bronchial carcinoma gave an overall take rate of 30–100%. Nevertheless, for the oat cell carcinoma (lowest overall take rate of 30%) at least one host accepted the xenograft in 60–70% of the primary tumours implanted. Subsequently, these tumours were passaged with a much higher take rate. Deprived mice may resist further stress less well than non-deprived animals and our experience suggests that they have reduced tolerance to chemotherapeutic agents.

Attempts to improve immune-deprivation of mice have led to investigation of: different timing of thymectomy: different timing between Ara-C and irradiation: use of higher radiation doses: use of BM reconstitution. Thymectomy at 3 weeks after birth produced better host acceptance of xenografts than thymectomy at 4–6 weeks. Once thymectomized, mice could be irradiated at any time (even several months later) without affecting their suitability. The percentage of animals accepting xenografts was highest when Ara-C was given 24–48 h before irradiation. Raising the radiation dose above 9 Gy improved the percentage of hosts accepting xenografts, but mortality was high, and the method was too unreliable to justify its routine use. Reconstitution with BM adversely affected tumour takes; a decrease in take rate resulted as increasing numbers of BM cells were given. A maximum of 2×10^5 cells per mouse is recommended when using BM reconstitution. Even at this dose, 26 weeks after irradiation only 53% of BM reconstituted hosts accepted xenografts, compared to 69% of Ara-C hosts. It was concluded that Ara-C treatment 2 days before 9 Gy of 3–4 weeks thymectomized mice remains the best deprivation schedule tested.