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Perspectives and Commentaries

Do We Need New Chemosensitive Experimental Models?

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THAT there is a need for new chemosensitive tumour models with higher yield in selecting new antineoplastic agents and better predicting the response of human cancers is self-evident. Indeed, the yield (the percentage of active drugs detected per model) of most chemosensitive murine tumours including the intramuscularly implanted M5076 reticulum sarcoma (M5) and even the ascitic P388 leukaemia is not satisfactory enough and many clinically active drugs would be missed if only one model was used to preselect new drugs for a secondary screening. Moreover, despite the progress in the identification of active antitumour agents by the animal screening models currently used, there is a real need for the discovery of new chemotherapeutic agents to treat and cure a number of human solid tumours against which the current chemotherapeutic drugs have not been significantly effective. The new intramuscularly transplanted M5 tumour does not seem to contribute much to the improvement of the yield required in a primary screening and to the clinical predictive capacity required in a secondary screening because it is insensitive to 5-fluorouracil, methotrexate and adriamycin while it responds to alkylating agents like most of the well-known tumour models.

It could be easily asserted that experimental tumour models are incapable of predicting efficacy in humans. However, the question is more complex, since human cancers, even when apparently similar, do not respond in a uniform manner to drugs: in spite of the apparent similarity, differences in the host and other still unrecognized factors are the explanation.

It is interesting to review the major possible reasons for the poor drug-activity correlation between human and animal cancers. These reasons are as follows:

(1) In contrast to certain infectious diseases, there is no common aetiology between experimental animal tumours and human tumours.
(2) There are no evaluable unequivocal data—except for asparaginase [1, 2]—establishing the presence of different biochemical pathways in tumour cells than in normal human or animal cells.
(3) The failure of animal models to predict positive drug responsiveness of human tumours may be due to differences in the total body burden of tumour cells at the time of drug treatment.
(4) The criteria for anticancer activity in the laboratory differ from those in the clinic and are often not comparable.
(5) Transplantable murine tumours are less differentiated than human cancers and their growth rate is accelerated.
(6) It is possible to administer drug doses up to the LD_{10} against animal models while similar doses cannot be used in humans.

At present, no objective approach to the first two above-mentioned points is available. However, to make a meaningful comparison between experimental and human anticancer activity, more attention should be given to points 3–6.

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In a preclinical investigation, animal treatment begins when the disease is at an early stage and not later than 24 hr after inoculation of a small number of tumour cells (10^6 cells/mouse). On the other hand, clinicians begin to treat their patients when the disease is diagnosed, i.e. when the body burden of tumour cells is higher than 10^8 and may amount to 10^{10} or 10^{11}. Experimentalists should do likewise and start treating when the disease is reasonably advanced and the body burden high enough. If they did so, experimental cancer chemotherapists could be not much more successful than the clinical oncologist in curing advanced malignancies.

Experimental and clinical criteria used to evaluate drug effectiveness must be alike. A 25% and even 50% increase in lifespan of tumour-bearing mice or a 50% inhibition of solid tumour growth often correlates with an increase—rather than a decrease—in body burden [3]. A high reduction of the number of tumour cells and a significant regression of the tumour mass are better criteria for a positive correlation.

Concerning point 5, it is desirable to introduce new validated either induced autochthonous or spontaneous tumour models with cell kinetic proliferation and metastatic patterns closer to those of human cancers than are multitransplanted murine tumours. The human tumour xenografts implanted subcutaneously in nude

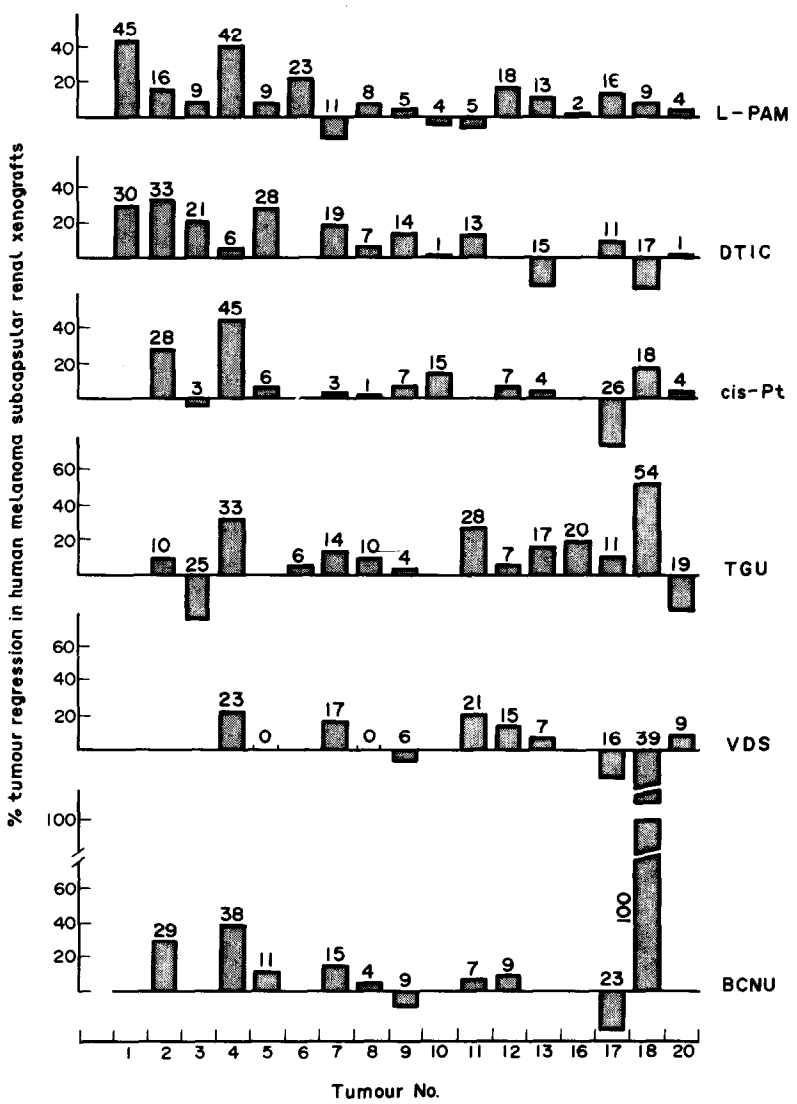

Fig. 1. Tumour chemosensitivity of fresh human melanoma xenografts in immunocompetent BDF1 mice. Tumour fragments were implanted under the renal capsule (Bogden technique). The fragments were measured in situ under magnification: the two largest diameters of the fragments were recorded on the day of transplantation in o.m.u. (10 o.m.u. = 1/10 mm). *Tumour size was expressed as the average of the two largest diameters. Drugs were administered i.v. on days 1–5. On day 6 tumour fragments were measured again and size variations were reported as the difference in size between days 6 and 0.*

athymic mice do not seem to provide better information than the murine tumours. The use of fresh surgical xenografts implanted under the capsule of the kidney of immunocompetent mice appears to be a good method of measuring activity towards a human tumour [4]. Furthermore, the feasibility of utilizing fresh surgical explants of human tumours as a first transplant generation to rapidly (6 days) determine the sensitivity to chemotherapeutic agents has already been demonstrated [5]. This technique is really time- and cost-saving. It also offers the possibility to predict the response to specific chemotherapeutic agents of individual tumours. Further histological investigations would secure a better selection of the day of evaluation. Fresh surgical xenografts from several patient donors may also reflect heterogeneous responses to a treatment while the established lines obtained from one individual donor would be either sensitive to most drugs investigated if the donor is sensitive to chemotherapy or resistant if the donor is resistant. Figure 1 clearly illustrates this problem: it shows the sensitivity of twenty fresh human melanoma xenografts to six chemotherapeutic agents. These fresh surgical implants originate from twenty donors. Figure 1 would suggest that if the tumour line is established from donor No. 20, the xenograft will show resistance to many anticancer agents while, if established from donor 4, the xenograft will show sensitivity. Established lines from one donor will not give newer information than the currently used murine tumour models. One should mention also the interesting human tumour cloning assay [6] used to evaluate drug sensitivity *in vitro*. In contrast with the *in vivo* subrenal assay, the microarchitecture of the tumour is destroyed and drug activity is evaluated by the response of a single-cell population. Moreover, drugs which need *in vivo* activation will be missed. However, the results obtained by the two methods may be complementary [7]. From a practical point of view, it is clear that these two models are useful in preclinical studies and less useful in a large new anticancer preselection program. As mentioned earlier, in a primary screening model the yield and sensitivity of the model are a major requirement to ensure the detection of a large percentage of active drugs, while in a secondary screening model the major requirement will be the capacity to predict clinical activity. Vandendris *et al.* [8] recently developed a murine renal carcinoma model with a relatively higher yield than the current models. Table 1 shows the sensitivity of the tumour in comparison with the L1210 and P388 leukaemias.

The dose aspect underlined in point 6 should also be taken into consideration. Non-toxic doses effective in reducing tumour growth are the most suitable, while optimal doses equal to or exceeding the LD_{10}—even when eliciting a 100% tumour growth inhibition—are meaningless. A good example is given by Langdon *et al.* [9], who brought into light the distinction between the ID_{90}, i.e. the dose inhibiting the tumour growth by 90%, and the optimal dose inhibiting tumour growth by 100%. In their study the ID_{90} of cyclophosphamide was 100 mg/kg, a safe dose much lower than the LD_{10} (370 mg/kg), while the optimal dose was 400 mg/kg. Obviously the equivalent of the latter optimal dose could never be used by clinicians.

Table 1. Sensitivity of the renal cell carcinoma to drugs inactive or marginally active against L1210 (LE) and P388 (PS) leukaemias

Compounds	RC	Effect LE	PS
Busulfan	++	-	-
op'-DDD	-	-	-
Hexamethylmelamine	++++	+	-
Bleomycin	++	-	±

-: no activity; +: ILS 25–49%; ++: ILS 50–99%; +++: ILS ⩾100%; ++++: ILS >100% + cures; ±: ILS not reproducible.

Finally, we may come to the conclusion that a good evaluation of the predictive value of experimental models used to detect new anticancer drugs cannot be carried out because clinical data are not available for drugs inactive in animal models [10]. However, it might be possible to improve the predictive value required for an experimental model and obtain a better correlation between experimental and clinical results by: (a) including in the current tumour panel induced autochthonous tumour systems with longer doubling time as well as fresh xenografts for adopting the parameters used in the clinic, namely partial or complete tumour regression, disease-free intervals and cures; and (b) investigating the host differences (e.g. in terms of metabolism and secretion) which may explain the differences in tumour responses to a drug and enable us to develop better models and methods with a better predictive value.

At the present time it would be premature to claim that we know the models to be used as *in vivo* screens for new anticancer agents and we need to continue our efforts to find more reliable tumour models for drug sensitivity of human cancer.

REFERENCES

1. Uren JR, Handnschumacher RE. Enzyme therapy. In: Becker FF, ed. *Cancer: a Comprehensive Treatise.* New York, Plenum, 1977, 457–487.
2. Burchenal JH. Success and failure in present chemotherapy and the implications of asparaginase. *Cancer Res* 1977, **29,** 2262–2269.
3. Schabel FM Jr, Griswold DP Jr, Laster WR Jr *et al.* Quantitative evaluation of anticancer agent activity in experimental animals. *Pharmacol Ther* 1977, **1,** 411–435.
4. Bogden AE, Haskell PM, Lepage DJ, Kelton DE, Cobb WR, Esber JH. Growth of human xenografts implanted under the renal capsule of normal immunocompetent mice. *Exp Cell Biol* 1979, **47,** 281–298.
5. Bogden AE, Costanza ME, Reich SD, Griffin TW, Cobb WR. Chemotherapy responsiveness of human breast tumors in the 6-day subrenal capsule assay: an update. *Breast Cancer Res Treat* 1983, **3,** 33–38.
6. Hamburger AW, Salmon SE. Primary bioassay of human tumor stem cells. *Science* 1977, **197,** 461–463.
7. Bogden AE, Von Hoff DD, Schwartz JH. Comparison of the human tumor cloning and subrenal capsule assays. *Proc ASCO* 1983, **2,** 3.
8. Vandendris M, Dumont P, Heimann R, Atassi G. Development and characterizations of a new murine renal tumor model: chemotherapeutic results. *Cancer Chemother Pharmacol* 1983, **11,** 182–187.
9. Langdon S, Gescher A, Hickman JA, Stevens MFG. The chemosensitivity of a new experimental model—the M5076 reticulum cell sarcoma. *Eur J Cancer Clin Oncol* 1984, **20,** 699–705.
10. Atassi G, Staquet M. The clinical predictive value of the mouse screening methods. In: Hilgard P, Hellmann K, eds. *Anticancer Drug Development.* Barcelona, Prous, 1983, 27–34.