Europ. J. Cancer, Vol. 16, pp. 289–291
© Pergamon Press Ltd. 1980. Printed in Great Britain

0014-2964/80/0201-0289 $02.00/0

Letter to the Editor

Different Growth Rates of Lung Tumours in Man and their Xenografts in Nude Mice

JÜRGEN MATTERN,* KLAUS WAYSS,* DIETER HAAG,† HEIKKI TOOMES‡ and MANFRED VOLM*

**Department of Experimental Pathology, German Cancer Research Center, Im Neuenheimer Feld 280, D-6900 Heidelberg*
†Department of Experimental Pathology, University of Heidelberg, D-6900 Heidelberg
‡Thorax-chirurgische Spezialklinik, D-6900 Heidelberg-Rohrbach, Federal Republic of Germany

In recent years the nude mouse has become of increasing value in the experimental research of human tumours and as a model system for chemotherapy of human cancer. Since this animal is congenitally athymic [1], it is unable to reject grafts of xenogeneic tissue. Thus, human tumours transplanted into the nude mouse grow easily without loss of original functions or morphology [2, 3].

Little is known, however, about the growth characteristics of such xenografts in nude mice. Since the rate of growth of tumours may influence their response to cytotoxic agents [4] and irradiation [5], it is important to know whether the cell kinetics of human tumours retain their characteristics after heterotransplantation and whether the growth of such xenografts is like that of the original tumour in the patient.

Accordingly, to answer these questions we have heterotransplanted in the course of a transplantation program 22 human lung tumours in nude mice (6–8 week-old female BALB/c nude mice). We noted progressive growth in 11 tumours (=50%), 7 of which were subpassed to further generations. Human tumour was received directly from the operating room, finely minced in the laboratory, diluted 1:3 with TCM 199, and 0.3 ml of the suspension was injected s.c. into the flank of 3 animals. In 4 patients the tumour doubling time could be determined by the method of Collins *et al.* [6] by measuring changes in tumour size from consecutive roentgenograms and the growth rates calculated were compared with the growth rates of the xenografted tumours in nude mice (Table 2, tumours 1–4). In animals the size of the tumours was measured biweekly with calipers and doubling time was also used to calculate growth rate.

In order to examine how the transplantation affects the growth rate of the xenografts in nude mice, the tumour doubling times of the growing tumours in different passages were determined. (Table 1). It is evident that the rate of tumour growth in-

Accepted 1 June 1979.

Table 1. Doubling time of human lung tumours growing in different passages in nude mice

Tumour No.	Histology	Tumour doubling time (days) Passage 1	2	3	4	5
1	Epidermoid	34	●			
2	Epidermoid	25	●			
3	Epidermoid	12	8	●		
4	Epidermoid	9	8	8	9	
5	Epidermoid	9	6	7	6	●
6	Adeno	6	5	3	4	2
7	Epidermoid	4	3	2	2	2

●—Further transplantation failed.

Table 2. Kinetic parameters of human lung tumours growing in nude mice

Tumour No.	Histology	Patient tumour Doubling time (days)	Patient tumour Cells in S-phase (%)*	Xenograft passage 1 Doubling time (days)	Xenograft passage 1 Cells in S-phase (%)
1	Epidermoid	62	20	34	n.p.†
2	Epidermoid	54	22	25	30
3	Epidermoid	29	23	12	35
4	Epidermoid	24	40	9	24
5	Epidermoid		12	9	45
6	Adeno		11	6	28
7	Adeno		17	—	28
8	Epidermoid		49	4	53

*The measurement were performed with a flow cytofluorometer (ICP22, Phywe, Göttingen).
†Preparation not possible.

creases during serial transplantation towards a limiting maximum value. The tumours with the longest doubling time (i.e., the more slowly growing tumours) could not be passaged into further generations. The increased tumour growth during serial transplantation causes the passage time to gradually decrease in successive passages.

The histological appearance of almost all of the tumours growing in the first passage in nude mice was in good agreement with that of the donor tumours. In further passages, however, a progressive dedifferentiation was noted in some tumours, depending on the growth rate of the tumours (unpublished results).

If the tumour doubling time of xenografts in the first passage is compared with the doubling time of lung tumours in man as reported in the literature [4], it is apparent that the xenografts in nude mice grow faster than do the tumours in the patients. The xenografts had a mean doubling time of 14 days in contrast to a mean doubling time of 87 days in lung tumours in man.

Table 2 lists the kinetic parameters of 8 lung tumours in man and their xenografts in nude mice. It is evident that the xenografts in nude mice grew faster than the original tumours did in the patients (tumour 1–4). With the exception of tumour 4, all other tumours in their first passage in nude mice had a higher proportion of S-phase cells than did the tumours in the patients.

In their xenograft lines from human colorectal tumours transplanted in immune deprived mice Pickard, Cobb and Steel [7] reported that the parameters of the cell cycle were similar to those that have been ascribed to tumours in man. If true, that would imply the acceleration of growth in nude mice is mainly due to an increased percentage of proliferating cells (perhaps together with a lower rate of cell loss). It should be emphasized, therefore, that an increase in the percentage of S-phase cells in xenografted tumour would make that tumour more susceptible to cytotoxic agents than the primary tumour in man [8] and thus, therapeutic results achieved with animals cannot be easily transposed to man.

REFERENCES

1. E. M. Pantelouris, Absence of thymus in a mouse mutant. *Nature (Lond.)* **217,** 370 (1968).
2. Y. Shimosato, T. Kameya, K. Nagai, S, Hirohashi, T. Koide, H. Hayashi and T. Nomura, Transplantation of human tumours in nude mice. *J. nat. Cancer Inst.* **56,** 1251 (1976).
3. J. Rygaard and C. O. Povlsen, Heterotransplantation of a human malignant tumour to nude mice. *Acta path. microbiol. scand.* **77,** 758 (1969).
4. S. E. Shackney, G. W. McCormack and G. J. Cuchural, Growth rate patterns of solid tumours and their relation to responsiveness to therapy. *Ann. intern. Med.* **89,** 107 (1978).
5. K. Breur, Growth rate and radiosensitivity of human tumours. *Europ. J. Cancer* **2,** 173 (1966).

6. V. P. Collins, R. K. Loeffler and H. Tivey, Observations on growth rates of human tumours. *Amer. J. Roentgenol.* **75,** 988 (1956).
7. R. G. Pickard, L. M. Cobb and G. G. Steel, The growth kinetics of xenografts of human colorectal tumours in immune deprived mice. *Brit. J. Cancer* **31,** 36 (1975).
8. M. Volm, L. Krieg, J. Mattern and K. Wayss, Effect of synchronization on chemotherapy of solid transplanted tumours. *Europ. J. Cancer* **13,** 1099 (1977).