THE Eu-myc TRANSGENIC MOUSE
A Model for High-incidence Spontaneous Lymphoma and Leukemia of
Early B Cells

BY ALAN W. HARRIS,* CARL A. PINKERT,† MARJORIE CRAWFORD,*
WALLACE Y. LANGDON,* RALPH L. BRINSTER,‡ AND JERRY M. ADAMS*†

From *The Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital,
Victoria 3050, Australia; and the †School of Veterinary Medicine, University of Pennsylvania,
Philadelphia, Pennsylvania 19104

Translocation of the c-myc protooncogene into or near one of the Ig loci is
found in almost every case of Burkitt's B cell lymphoma in man and experimentally
induced plasma cell tumor in the mouse (reviewed in references 1, 2). This
accidental rearrangement of the cellular genome appears to free the c-myc gene
from its normal susceptibility to negative regulation and to render it constitutively
active in cells that express Ig genes (reviewed in references 1–4). The contribu-
tion of the rearranged gene to the neoplastic phenotype may stem from the
ability of the myc polypeptide to drive cellular proliferation, perhaps by promoting
DNA replication (5, 6). While its biochemical function is not yet defined, c-myc
expression normally correlates closely with cell-cycle activity in a broad range of
cell types, increasing greatly when resting cells are mitogenically stimulated and
declining when they cease to proliferate (3, 4, 7).

The effects of altered oncogenes on cells in their natural environment can be
assessed through the use of transgenic mice (8, 9). A transgenic strain is initiated
by inserting a gene into the mouse genome and is perpetuated thereafter by
normal breeding. By this means, a c-myc gene coupled to regulatory sequences
from the mouse mammary tumor virus was shown to cause mammary carcinomas,
and sometimes other tumors, after a substantial latent period (10, 11). To mimic
the translocated myc genes found in lymphoid tumors, we introduced into mice
a DNA sequence, designated Eu-myc, isolated from a mouse plasmacytoma in
which a normal myc gene had become coupled to the Ig heavy chain enhancer
(12). In the resultant transgenic mice, the Eu-myc transgene appears to be
expressed exclusively in B-lymphoid cells (13) and causes them to proliferate
more than normal (14). Starting before birth, the pre-B cell population expands
progressively up to about five times its normal size, while B cells are somewhat
reduced in number despite their increased cell-cycle activity (14). The immune

This work was supported by the National Health and Medical Research Council, Canberra, and the
Drakensberg Trust; by generous gifts from the Estate of Victor Lawford and the Helen M. Schutt
Trust; and by grants from the U.S. National Institutes of Health (CA-45540, CA-12421, HD-09172,
and CA-38635) and the American Heart Association. C. A. Pinkert was a trainee on HD-07155; his
present address is Dept. Animal Sciences, University of Missouri, Columbia, MO 65211. Address
correspondence to Dr. A. W. Harris, Walter and Eliza Hall Institute, P.O. Royal Melbourne Hospital,
3050, Australia.
responsiveness of \( E\mu\)-myc animals is not greatly affected by these perturbations (15). Thus, the excessive proliferative activity induced by the \( E\mu\)-myc gene is limited and benign. However, these mice also develop lymphomas of B-lineage cells (16).

To establish the \( E\mu\)-myc mouse as a model of lymphomagenesis, we here quantify the incidence, pathology, and cell surface phenotypes of the tumors. Despite some variation in the pathology, all of the tumors have proven to be malignant lymphomas of B-lineage cells, usually accompanied by lymphoid leukemia. We compare them with other mouse lymphomas and with the tumors that characterize the SJL strain, a contributor to the genetic background of the transgenic line. We also describe a characteristic of the blood of young \( E\mu\)-myc mice that provides a rapid means of distinguishing them from normal mice.

A notable feature of these mice is that lymphomagenesis has proven to be virtually inevitable. Nevertheless, individual tumors appear to initiate at random with age. Analysis of the kinetics of tumor onset allows us to estimate the rate of malignant conversion within the susceptible cell population.

**Materials and Methods**

**Mice.** Primary transgenic mice and initial breeding lines were produced by the techniques of Brinster et al. (17, 18) using the \( E\mu\)-myc DNA construct specified by Adams et al. (16), and (C57BL/6J \( \times \) SJL/J)F\(_2\) embryos descended from inbred mice purchased from The Jackson Laboratory (Bar Harbor, ME). For subsequent detailed analysis, the \( E\mu\)-myc 292-1 transgenic line was propagated by breeding (heterozygous) transgenic males with normal (C57BL/6JWehi \( \times \) SJL/JWehi)F\(_1\) hybrid (BSJF1)\(^3\) females. As expected, ~50% of the progeny were transgenic. Transgenic females were not generally used for breeding because of their high risk of developing lymphomas before their pups reached weaning age. Animals used for assessing tumor onset kinetics were produced by mating multiple BSJF1 females with 4 third-generation transgenic males to randomize the contributions of C57BL and SJL traits. At 3 wk of age, the progeny of BSJF1 \( \times \) transgenic matings were segregated by gender and numbered by ear punching. To identify transgenic pups, DNA extracted from tail tips (18) was hybridized with \( ^{32}\)P-labeled pUC12 plasmid DNA, sequences of which were present in the introduced \( E\mu\)-myc construct (16). An alternative test using blood cell nuclei is described below. When it was necessary to retest older animals for transgene carriage, DNA was extracted either from a skin biopsy or from the liver after sacrifice.

The mice were maintained under clean conventional conditions with free access to 2.5 Mrad-irradiated mouse breeder ration cubes (Barastoc Stock Feeds,Victoria, Australia) and acidified filtered tap water (3 mM HCl).

**Monitoring Tumor Development.** At weekly intervals after weaning, each mouse was closely inspected and its inguinal lymph nodes were palpated to detect enlargement. Any animal with an overt tumor was examined more frequently so that it could be autopsied when it became ill. For histology, soft tissues were fixed in Bouin's solution, bony tissues in neutral buffered 10% formalin. Paraffin-embedded fixed tissues were sectioned 4 \( \mu \)m thick and stained with hematoxylin and eosin.

**Electronic Counting of Cells and Sizing of Nuclei.** The equipment comprised a Zm Counter and C1000 Chronelizer (Coulter Electronics Ltd., Luton, United Kingdom) connected to a microcomputer. These units were interfaced and programmed by Dr. F. Battye of the Walter and Eliza Hall Institute Flow Systems Laboratory. The system was calibrated with 9.7 \( \mu \)m polydivinylbenzene latex (Coulter Electronics Ltd.) and verified electronically for linearity of response.

Leukocytes were counted and sized as nuclei, obtained by adding the cell lysing agent, Zaponin (Coulter Electronics, Ltd.), to diluted blood. The diluent was PBS containing 5 mM KCl and adjusted to mouse tonicity (305–310 mosmol/kg). Blood was obtained from
the retroorbital sinus using heparinized capillaries, or by cardiac puncture from animals anesthetized intraperitoneally with tribromoethanol. For routine typing of weanling mice for enlarged leukocyte nuclei (see Results), 5 μl of retroorbital blood was diluted into 20 ml of diluent and 6 drops of Zaponin were added just before the Coulter Counter analysis. The particle volume range used for counting and sizing was 22–110 fl.

**Cell Surface Antigen Expression.** The presence of Thy-1, Ly-5(B220), and Ig antigens on cells dispersed mechanically from tumors was detected by flow cytometric analysis of immunofluorescence as described (14).

## Results

**Lymphomas in Primary Transgenic Mice and their Descendants.** The Eμ-myc construct was highly tumorigenic in independent transgenic lines. Of 15 primary transgenic mice that developed from eggs microinjected with the Eμ-myc construct, 12 became ill with lymphomas at 6 to 14 wk of age. Of the other 3, one was found cannibalized at 6 wk, another died at 34 wk without gross evidence of lymphoid pathology, while the third, which remained healthy for more than a year, was suspected of mosaicism from the low rate (2/13) at which the transgene was transmitted to its progeny. From five of the primary animals, breeding lines were initiated through matings with normal BSJF1 mice. All their transgene-bearing progeny developed lymphoid tumors, almost all becoming ill at 6–18 wk of age. The median onset of illness was 11 wk for the whole pool of 12 primary and 41 second- and third-generation animals. It varied only between 10 and 13 wk in the five separate lines. Consequently, one of the lines (denoted 292-1) was arbitrarily selected for long-term breeding and detailed investigation.

**Tumor Onset and Progression.** Tumor development was assessed in the entire fourth generation of the Eμ-myc 292-1 line (134 animals). In 83% of animals the first sign was enlargement of one or both inguinal lymph nodes, detected by palpation. A few mice died unexpectedly, but the others were killed for autopsy when they became ill, as manifest by hunched posture, slow movement, ruffled fur and, often, tachypnea.

The time course of disease varied markedly between individuals, in both the age at which the first signs appeared and the rate of progression to illness or death (Table I). The male and female incidence was equivalent (not shown). The onset of first externally detectable signs and of terminal illness as functions of age are plotted as semi-log "survival" curves in Fig. 1. The curves appear to have three components (see Discussion). A major portion of the population (~70%) produced a plot closely approximating a simple exponential over the age range from 6 to ~16 wk, so that the frequency of appearance of new tumor cases

### Table I

**Time Parameters of Tumor Development**

| Event                        | Median Age | Age Range |
|------------------------------|------------|-----------|
| Pathology onset              | 9 wk       | 3–81 wk   |
| Illness or death             | 12 wk      | 6–83 wk   |
| Progression from first signs to illness or death | 25 ± 19 d | 0–94 d |

134 mice from the fourth generation of the Eμ-myc 292-1 line were monitored for tumor development as described in Materials and Methods.
LYMPHOMA AND LEUKEMIA IN Eμ-myC MICE

FIGURE 1. Onset of tumors and appearance of terminal illness with age in Eμ-myC mice. The first sign of lymphoma was designated as "onset" and ill health (or actual death) as "death." Regression lines were calculated for the ranges of "onset" data points indicated. Data from 70 females and 64 males (as in Table I) were pooled.

| Feature                                      | Incidence |
|----------------------------------------------|-----------|
| Enlarged lymph nodes and spleen              | 84*       |
| Tumor (or swelling) on thoracic vertebral column | 68       |
| Enlarged thymus (threefold or more)          | 54        |
| Bowel obstruction                             | 13        |
| Hind limb paralysis                           | 1.5       |

134 Eμ-myC mice (as in Table I) were autopsied when ill or after natural death.

* The 16% without general enlargement of lymph nodes comprised nine cases of thymoma, five of intussusception, four with a single large lymph node, and four with no grossly visible pathology.

among hitherto healthy animals (the hazard rate) was constant at 17% per week. The "death" curve was displaced by about 5 wk and was parallel. Below 5 wk of age, the hazard rate was lower and progression slower, terminal illness requiring an average of 5 wk to develop. Animals that remained free of disease for more than ~17 wk were subject to a reduced hazard rate of ~6% per week. Once initiated, their tumors progressed rapidly to terminal illness in 1–3 wk.

Lymphomatosis is an essentially inevitable fate for Eμ-myC mice. >90% had succumbed within 6 mo. By 1 yr only two of the original 134 animals remained healthy. One was found cannibalized at 65 wk, and the other developed tumors at 81 wk of age.

Gross Pathology. Dissections revealed gross evidence of disseminated lymphoma in all but 4 of the 134 animals. Typically, most or all lymph nodes were enlarged 5–50-fold and the spleen 2–6-fold (Fig. 2, A and B). Enlargement was usually similar in bilaterally paired lymph nodes. Frequencies of particular autopsy findings are given in Table II.

A majority of animals showed substantial enlargement of the thymus, in at least some cases clearly distinct from the three enlarged mediastinal (parathyMIC) lymph nodes adjacent to it. In nine of the animals, a thymoma was the dominant abnormal tissue mass (Fig. 2C). Another common finding in the thorax was a
FIGURE 2. Dissections of Eμ-myc mice with advanced tumors and of BSJF1 mice bearing transplanted Eμ-myc tumors. (A) 13-wk-old Eμ-myc mouse with typical enlargement of lymphoid organs including the Peyer's patches and the thymus (× 0.7); (B) same animal after removal of loose abdominal and thoracic organs to reveal greatly enlarged renal and lumbar lymph nodes and thickening of thoracic vertebral column (× 1.1); (C) 9-wk-old Eμ-myc mouse with large thymoma but near-normal lymph nodes (× 0.9); (D) 11-wk-old Eμ-myc mouse with top of skull hinged open to show layer of tumor adhering to the parietal and interparietal bones (× 2.2); (E) BSJF1 animal, 35 d after injection intraperitoneally and subcutaneously of 100 mesenteric lymph node cells from a lymphomatous Eμ-myc mouse, showing a large tumor mass at the site of injection (left), a flat subcutaneous mass on the contralateral side, and enlarged lymph nodes, thymus and spleen (× 0.9); (F) BSJF1, recipient of 10⁶ femoral bone marrow cells from another primary tumor mouse, showing flat subcutaneous masses near the axillae, enlarged lymph nodes and thymus, tumor tissue around the heart, and some thickening of the thoracic vertebral column (× 1).

visible swelling along the vertebral column (Fig. 2B), sometimes in the form of a discrete tumor terminating anterior to the diaphragm. In some animals, the Peyer's patches were enlarged (Fig. 2A). Tumor growth within the wall of the small bowel presumably caused the bowel obstruction found in 13% of the animals. This usually took the form of intussusception, which rapidly caused terminal illness. About one-quarter of all the animals had tumor masses inside the skull adherent to the parietal and interparietal bones (Fig. 2D), occasionally
FIGURE 3 A–F.
large enough to deform the skull and depress the cerebrum and cerebellum. The other major organs with visible abnormalities were the liver, which was often enlarged (up to twofold); the lungs, which occasionally had a few presumptive tumor deposits; and the skin, which sometimes showed flat masses of tumor
spreading posteriorly from the axillary region, presumably through mammary tissue.

**Histopathology.** Histologic examination of 60 animals with advanced tumors revealed tumor cells within many tissues. In the enlarged lymph nodes, the normal architecture was largely obliterated. Normal cells were almost completely replaced by medium-sized cells with little cytoplasm and open-looking, often indented, nuclei containing large nucleoli and fine reticular chromatin, i.e., lymphoblasts (Fig. 3A). The thymus appeared similar (Fig. 3B), even in some of the mice in which it was not grossly enlarged. The cortex tended to be more densely packed with lymphoblasts than the medulla. In one case the thymus was normal except for patches of abnormal lymphoblasts in the cortex, presumably representing an early stage of thymic invasion by tumor cells.

The spleen and bone marrow were altered even in young healthy Eμ-μc mice. The pretumor spleen was up to twice normal size, and its red pulp showed greatly increased extramedullary hematopoiesis, with many more megakaryocytes and nucleated erythroid cells, albeit less erythrocytes than normal. Many lymphoblasts were scattered through the red pulp (but were not apparent in the white pulp). In terminally ill animals, the red pulp sometimes contained more abundant lymphoblasts, which largely or completely replaced normal lymphocytes in the white pulp (Fig. 3C). Pretumor bone marrow was dominated by pre-B lymphoblasts (14). In the femoral marrow of animals with advanced lymphoma, there was often a further increase in the number, and sometimes the size, of lymphoblasts, although general hematopoietic activity was never completely displaced (not shown).

In tumorous animals, the liver was routinely invaded by lymphoblasts, which formed variable-sized masses in portal areas, and sometimes infiltrated the liver parenchyma, occupying the sinusoids of the lobules (Fig. 3D). While none of 8 kidneys examined histologically showed invasion, lungs from 17 diseased animals all showed widespread diffuse infiltration of the alveolar septa by lymphoblasts. The resulting partial collapse of the alveolar air spaces (Fig. 3, E and F) may have caused the tachypnea commonly suffered by animals with advanced tumors. Lung lymphatic vessels were sometimes strikingly distended by a glut of lymphoblasts, and major blood vessels commonly contained large numbers, indicative of lymphoblastic leukemia (see below). In some cases the pleura contained discrete masses of lymphoblasts (Fig. 3E).

Muscle and bowel were sometimes involved. Cardiac muscle was occasionally penetrated (Fig. 3G), while intercostal muscle was extensively infiltrated by the lymphoblasts accumulated along the thoracic vertebral column (Fig. 3H). However, neither these swellings nor the tumor deposits under the roof of the skull (Fig. 3I) ever reflected any infiltration of the spinal cord or the brain. In the digestive tract, apart from a single cecal lymphoma, lymphoblasts were prevalent only in Peyer’s patches. When gross enlargement occurred, there was intrusion into the lumen (Fig. 3J) and, in cases of intussusception, a lymphoblast-packed Peyer’s patch could often be seen at the head of an everted portion of bowel, drawn by peristalsis into the adjacent bowel (Fig. 3K).

**Transplantability.** To verify that the masses of lymphoblasts seen in the enlarged lymphoid tissues of Eμ-μc mice were malignant, up to $10^6$ cells from
Transplantability of $E_{\mu}$-myc Tumor Cells

| Donor animal | Donor tissue* | Days until first sign of tumor growth at cell numbers per recipient of: |
|--------------|--------------|-------------------------------------------------|
|              |              | $10^5$  | $10^4$  | $10^3$  | $10^2$  | $10^1$  |
| F-527        | Mesenteric lymph node | 18 | 18 | 21 | 26 | 21 |
|              |              | 26 | 26 | 26 | 26 | 26 |
| F-527        | Femoral bone marrow | 18 | 21 | 21 | 26 | 21 |
|              |              | 26 | 26 | 26 | 26 | 26 |
| F-546        | Mesenteric lymph node | 10 | 13 | 13 | 17 | 17 |
|              |              | 10 | 17 | 17 | 17 | 17 |

* Tissues were taken from seventh generation $E_{\mu}$-myc mice with advanced lymphoma.

Transplantation titrations, in which cells from four donors were reduced in 10-fold steps from $10^5$ to $10^1$ cells per recipient, yielded tumors at all cell doses. Examples are shown in Table III. Irrespective of dose, all tumors arose within 10–30 d.

With a few exceptions, the gross pathology (Fig. 2, E and F) and histopathology (not shown) in transplant recipients was similar to that in the primary tumor animals. Depending on the donor, tumor growth at the site of subcutaneous injection varied from undetectable to very large masses, but was almost always accompanied by enlargement of the lymph nodes, the spleen, and the thoracic tissue around the vertebral column, and by infiltration of the thymus, the bone marrow, the liver, and the lungs. The blood was leukemic and granulocytotic. Transplant recipients did not, however, develop subparietal tumors or intussusception, and enlarged Peyer's patches were rare.

Selective homing patterns were not evident. For example, cells from primary thymomas did not predominantly cause thymic enlargement in recipients, and cells from two subparietal tumors did not produce visible growth inside the skull. On the other hand, one large primary subparietal tumor that showed little spread to other organs produced massive tumor growth only at the subcutaneous injection site, presumably reflecting its heritable inability to metastasize.

Transplantation provides a sensitive test for the presence of malignant cells before overt tumors. We examined 149 $E_{\mu}$-myc mice, between 4 and 10 wk of age, that appeared free of disease. Dissection revealed that 23 (15%) had enlarged lymph nodes and/or an enlarged thymus. 79 of the others were tested for malignant cells by transplanting $1–5 \times 10^6$ bone marrow cells from both femurs and, from some of these donors, $5–20 \times 10^6$ spleen and mesenteric lymph node...
LYMPHOMA AND LEUKEMIA IN Eμ-myc MICE

TABLE IV

Leukocytes of Lymphomatous and Prelymphomatous Eμ-myc Mice and Nontransgenic Littermates

| Parameter                              | Nontransgenic | Pretumor | Early tumor | Terminal tumor |
|----------------------------------------|---------------|----------|-------------|----------------|
| Nucleated cells (× 10⁶/ml)             |               |          |             |                |
| Range (number of samples)              | 1.5-8.1 (22)  | 2.5-11 (10) | 3.0-41 (17) | 3.7-130 (17)   |
| Geometric mean ± SD                    | 4.2 ± 1.6     | 5.7 ± 1.7 | 11 ± 2.5    | 29 ± 4.0       |
| Mean nuclear volume (fl)               | 57.4 ± 1.0    | 39.6 ± 1.4 | 49.2 ± 6.6  | 52.9 ± 6.5     |
| Polymorphs (Percent of nucleated cells) |               |          |             |                |
| Range (number of samples)              | 6-17 (15)     | 3-20 (10) | 4-54 (16)   | 5-45 (13)      |
| Mean ± SD                              | 11.4 ± 5.5    | 10.1 ± 5.2 | 14.2 ± 7.4  | 19.5 ± 15.2    |
| Polymorphs (× 10⁶/ml)                  |               |          |             |                |
| Range (number of samples)              | 2-8 (15)      | 2-14 (10) | 5-49 (16)   | 4-180 (13)     |
| Geometric mean ± SD                    | 4.2 ± 1.7     | 5.2 ± 1.8 | 14 ± 2.1    | 28 ± 5.1       |

Animals of both sexes aged 6-21 wk in the terminal tumor group and 5-11 wk in the other three groups were bled from the heart or the retroorbital sinus.

* Diluted heparinized blood was treated with Zaponin (Coulter Electronics) and the lysed-cell nuclei were counted and sized using a Coulter Counter and Channelizer (see Materials and Methods).

§ Giemsa-stained blood smears were scored for polymorphs as a percentage of 200-400 nucleated cells.

Concentrations were calculated from each percentage and the corresponding Coulter count of nuclei.

cells, by subcutaneous and intraperitoneal injection into normal B6SJF1 mice. Within 2 mo, eight had generated disseminated lymphomas in the recipients, all of which were observed for at least 3 mo. Thus, overall, 24% of ostensibly healthy transgenic animals were actually in early stages of lymphoma development.

Blood Leukocytes. The lymphoblasts in sections of blood vessels from animals with advanced lymphoma indicated that the disease had a leukemic component. The development of leukemia was therefore investigated by microscopic examination of blood smears and by counting and sizing blood cell nuclei in a Coulter Counter. Terminally ill animals and those at an early stage of tumor development were compared with pretumor young adult Eμ-myc animals and their nontransgenic littermates.

Table IV shows that, although white-cell parameters varied greatly within each group, there were clear differences between the four groups. On average, pretumor animals had somewhat more cells and slightly larger nuclei than the nontransgenic controls. The blood of most lymphomatous animals, however, contained markedly more cells and larger cell nuclei (Table IV), and stained smears revealed large lymphoid cells (Fig. 3L), even when the total leukocyte count was within the normal range. Clearly, though, the extent to which these lymphoblasts invaded the circulation varied greatly in both early and late stages of tumor growth in different animals. Fig. 4 depicts examples of nuclear size distributions from which the mean volumes were computed. The profiles from lymphomatous animals (Fig. 4, e-f) were all distinguishable from those from healthy animals (Fig. 4, a and b), but appeared to vary in the relative proportions of nuclei of two sizes, centered on ~35 and ~60 fl.

Leukemic blood frequently had more abundant granulocytes (Table IV and Fig.3L). 10 of 13 advanced cases scored for these cells had levels higher than
HARRIS ET AL.

FIGURE 5. Leukocyte nuclear size in weanling \( E\mu\)-myc mice and nontransgenic littermates. 10 litters (71 mice), born of normal females mated to \( E\mu\)-myc males, were tested for transgene carriage by tail DNA hybridization and were bled for determination of mean leukocyte nuclear volume at 21-27 d of age. Filled areas indicate transgene-positive animals, open areas transgene-negative animals. Nuclear volumes were measured on Zaponin-lysed blood with a Coulter Counter and Channelizer.

FIGURE 4. Size distributions of leukocyte nuclei from normal and from \( E\mu\)-myc mice. The animals, the mean volumes of their leukocyte nuclei, and their leukocyte counts were: (a) 42-d nontransgenic, 37 fl, \( 8.1 \times 10^6 \)/ml; (b) 42-d \( E\mu\)-myc pretumor, 40 fl, \( 11 \times 10^6 \)/ml; (c, d, e, and f) \( E\mu\)-myc mice with advanced lymphoma, 48, 59, 52, and 51 fl, 88, 48, 4.5, and \( 130 \times 10^6 \)/ml, respectively. Counts and volumes were derived from Zaponin-lysed blood with a Coulter Counter and Channelizer.

the maximum in the 15 control animals tested. The granulocytosis presumably is a response to tumor cells, since it developed also in BS/F1 animals carrying transplanted lymphomas (not shown).

**Rapid Identification of \( E\mu\)-myc Mice.** In producing large numbers of transgenic animals, it becomes very time-consuming to identify the transgenic progeny of heterozygous parents by DNA hybridization. The slightly enlarged leukocyte nuclei in young adult \( E\mu\)-myc mice (Table IV), together with our earlier finding that B-lymphoid cells in these animals cycle more than normal (14), led us to test whether they could be identified at weaning (3 wk) by size measurements on blood leukocyte nuclei. Fig. 5 compares the frequency distribution of mean nuclear size with results of tail DNA hybridization tests on 21- to 27-d pups. Fortunately, the nuclear size difference was accentuated at this age. Despite the spread of values in the normal group (Fig. 5, open bars) and the apparent bimodality in the transgene-positive group (Fig. 5, solid bars), >90% could be confidently classified by this rapid test, which requires only 5 \( \mu l \) of blood (see Materials and Methods). Subsequent routine tests on several hundred weanlings have confirmed that mean nuclear volumes above 43 fl are reliably diagnostic of transgene carriage and below 42 fl of normality. Weanlings with values of 42 or 43 fl are either retested by DNA hybridization or discarded.

The concentration of leukocytes was also elevated in most weanling \( E\mu\)-myc mice. While 90% of normal weanlings had from 4 to \( 10 \times 10^6 \)/ml, their transgenic littermates had \( 8.5-50 \times 10^6 \)/ml with a median of \( 19 \times 10^6 \)/ml. Therefore, cell counts identify most transgenic animals, but nuclear volume has proven more
discriminating. Comparison of the data from young adults (Table IV) and from weanlings (Fig. 5) reveals that early in the life of an Eμ-myc mouse there is a transient flood of enlarged leukocytes into the circulation. These cells have lymphoid morphology in stained smears (not shown).

Immunologic Classification of Tumors. Since the tumors consisted of lymphoblasts, they would be classified as lymphoblastic lymphomas, but tumors of this morphology can derive from either the T or the B lineage (19). Therefore, cells from primary lymphomas were tested for staining with fluorescent antibodies against the T cell marker Thy-1 and the B-lineage markers Ly5(B220) and Ig. None of 31 tumors tested bore Thy-1, not even the thymic cells from six animals with dominant thymoma. 6 of the 31 showed surface expression of Ig on essentially all cells, while another 9 contained mixed populations of tumor cells ranging from 5% to 87% surface Ig^+_. Of 16 Thy-1^- tumors tested for the Ly-5(B220) surface antigen, 15 were positive. In addition, primary tumors and cultured tumor cell lines all carry rearranged Ig genes (16; Cory, S., A. W. Harris, W. Y. Langdon, and J. M. Adams, manuscript in preparation). Thus all Eμ-myc tumors appear to derive from the B-lineage, pre-B lymphomas and mixed pre-B/B lymphomas predominating.

Tumors in Nontransgenic Mice. Middle-aged SJL mice develop a tumor known as reticulum cell neoplasm, type B (20). Because the Eμ-myc animals contained a variable assortment of genes of SJL (and of C57BL) origin, we assessed the incidence and nature of tumors arising in a group of >100 of their nontransgenic littersmates. No tumors were found until 10 mo, when one mouse was killed with a disseminated lymphoma, and two others began to develop slowly progressing tumors. 10 of the 105 animals surviving the first year were killed during the following 6 mo with advanced tumors in lymphoid organs, and 21 others were killed (sick, or with fight wounds) without evidence of neoplasia. When the 75 survivors were autopsied at 18 mo of age, 25 had one or more enlarged lymphoid organs. The estimated tumor incidence in the 12- to 18-mo age range was 37% (35/95).

The gross pathology varied, partly because a third of the tumorous animals were killed while apparently healthy, but the most frequent findings were greatly enlarged mesenteric lymph nodes (83%) and large spleens (69%) (Fig. 6A). In 16 of the 36 tumor-bearing animals (44%), one or more Peyer's patches were enlarged (Fig. 6A). Widespread lymph node enlargement was found only in sick animals and probably is a late event in tumor progression.

None of the 31 tumors from nontransgenic animals examined histologically were lymphoblastic lymphomas. A few comprised fairly uniform masses of large lymphoid cells with moderate amounts of faintly staining cytoplasm and probably were follicular center cell lymphomas. Most tumors, however, were highly varied mixtures of lymphoid and nonlymphoid cells, like those described as reticulum cell neoplasm, type B (21). The mesenteric lymph node was replete with such cells, often including distinctive giant multinucleate cells (Fig. 6B). The large nodular spleen (Fig. 6C) contained greatly enlarged white pulp areas filled with tumor cells, and increased hematopoiesis in the red pulp. The lungs contained discrete tumor nodules (Fig. 6C).

This histologic picture held for only two of the 134 Eμ-myc animals, one of
FIGURE 6. Gross pathology and histopathology of tumors in nontransgenic B6SJF1-backcrossed mice. The animals commonly exhibited (A) enlarged mesenteric lymph node and Peyer's patch(es) and an enlarged, nodular spleen (× 1.9); (B) mesenteric lymph node containing an abnormal mixture of cells including a giant multinucleate cell (× 600); and (C) lung containing dense nodular deposits of tumor cells (× 60).
which succumbed at 42 wk of age with both reticulum cell neoplasm, type B and lymphoblastic lymphoma. The other, the longest surviving confirmed transgene carrier, became ill at 83 wk of age with reticulum cell neoplasm, including nodular lung deposits. This unfortunate animal had won a Pyrrhic victory against the high odds of developing a lymphoblastic lymphoma!

Discussion

We have characterized the \( E\mu-\text{myc} \) mouse in some detail as a model for lymphoid tumorigenesis. After a variable period during which there is a benign, limited overgrowth of pre-B cells (14), essentially every mouse develops tumors. Although the disease manifestations are somewhat variable in detail (Table II and Fig. 2), the dominant picture is disseminated lymphoma. The morphology of the tumor cells, and the almost invariant infiltration of the lungs and liver (Fig. 3, D, E, and F) fit the classification of lymphoblastic lymphoma in the Pattengale-Taylor (19) scheme for mouse lymphoid tumors.

Lymphoblastic lymphomas of mice can derive from either the T or the B lineage (19). An enlarged thymus is usually indicative of a T lymphoma, such as those that arise in AKR and C58 mice, or in other strains given Moloney leukemia virus or x rays (e.g., reference 22). Thymic enlargement was common in \( E\mu-\text{myc} \) mice with advanced tumors (Table II), and in 9 of 134 it was the dominant abnormality at autopsy. Nevertheless, all these proved to be B-lineage tumors, mostly pre-B lymphomas. Since pre-B cells are not found in the prelymphomatous thymus (14), and since the lymphoma cells commonly metastasized to the thymus after transplantation, we assume that the primary thymomas were caused by invasion from outside the thymus. The same argument applies to the lymph nodes and leads us to suggest that acquisition by pre-B cells of the ability to invade the thymus and lymph nodes is a critical step in tumor development. Some other B-lineage tumors are known to metastasize to the thymus to a limited extent, including B-immunoblastic lymphomas (23) and the B-lymphocytic leukemia line BCL1 (24). The pre-B lymphoblastic lymphomas induced by Abelson virus, on the other hand, never appear to involve the thymus (25, 26).

Features common to Abelson and \( E\mu-\text{myc} \) tumors, apart from the enlarged lymph nodes and spleen common to most mouse lymphomas, are the deposits inside the skull and along the vertebral column. It has been postulated that these prominent features of Abelson disease are formed by cells emerging from the marrow of adjacent bones (26). With advanced \( E\mu-\text{myc} \) tumors, vertebral column swelling by lymphoma cells was common; tumors inside the skull much less so. Recipients of transplanted cells did not develop skull tumours, but usually did show paravertebral tumor and bone marrow invasion. Thus, pre-B lymphoma cells can readily metastasize from the periphery to the tissues along the vertebral column, although this could involve an intermediate sojourn in the regional bone marrow.

The rate of appearance of tumors in \( E\mu-\text{myc} \) mice is not constant throughout life (Fig. 1). In the first few weeks it averages \( \sim 5\% \) per week, later increasing to \( 17\% \) per week and finally falling again to \( 6\% \) per week. The low initial rate may reflect a smaller number of cells at risk of malignant transformation in the young growing animal. It is also possible that the differing rates manifest the presence
of genetically determined subpopulations of animals, since the genetic background is a segregating mixture of C57BL and SJL alleles. From ~6 wk of age, when adult size is neared, the tumor onset rate is constant at 17% per week for ~70% of the animals. This corresponds to a mean time of 38 d for a malignancy-initiating event in mice of 6–16 wk of age. Animals remaining free of tumor for longer periods appear to represent a relatively resistant subpopulation with an onset rate of only 6% per week and a mean time of 108 d to initiation of malignancy. This reduced rate is associated with a reduced expansion of the pre-B cell population in the pretumorous animals (14), and appears to be genetically determined. Preliminary results from serial backcrossing with inbred C57BL/6J mice indicate that one or more C57BL genes confer a relative resistance to transgene-associated lymphomagenesis (Harris, A. W., unpublished observations).

Since early-onset tumors did not progress more rapidly than late-onset tumors (Fig. 1), the early tumors are not simply the more aggressive ones. Instead, the random onset must be related to the appearance of the first malignant cell within each animal. That cell must be generated by a low-frequency event, presumably a genetic accident, within the abnormally expanded pre-B population. We can estimate the frequency of malignant conversion. The young adult Eμ-myc mouse contains ~2.4 × 10^8 pre-B cells, most of which are in a proliferative state (14). If half these cells divide on average every 8 h, like the cycling subset of pre-B cells in a normal mouse (27), then in the 38 d required for each tumor-initiating event to occur, the total pre-B pool will have undergone about 10^10 cell divisions. Thus, the rate of occurrence of malignancy-inducing events is about 10^-10 per cell per generation. This is an exceptionally low rate for a single mutation. Perhaps only certain extremely specific mutations suffice, or perhaps even a dysregulated myc gene-expressing pre-B cell requires two mutations to become a malignant cell. Another possibility is that most newly mutated potentially malignant cells are eliminated by the mechanisms responsible for the rapid turnover of pre-B cells before their mutant phenotype can be effectively expressed.

The high transplantability of the primary lymphomas (Table III) implied that transplantation might reveal malignant cells in transgenic animals not yet exhibiting signs of lymphoma. When many such animals were examined internally for lymphoid organ enlargement and tested for transplantable tumor cells, 24% proved to be in early stages of lymphoma development. By relating this figure to the tumor onset rate of 17% per week, we conclude that lymphomas actually initiate in Eμ-myc mice an average of 10 d before externally recognizable signs become apparent.

We found that the Eμ-myc mice develop leukemia as well as lymphoma. Although other mouse lymphoid malignancies are commonly called leukemias, it is difficult to find published quantitative data on the blood cells, and qualitative statements (e.g., references 19, 25, 26, 28) suggest that those tumor models do not develop the high concentrations of circulating tumor cells that can occur in human leukemias. An exception is the mouse chronic B-lymphocytic leukemia BCL11, which yields blood concentrations 10–30 times above normal leukocyte levels (24). Abelson pre-B lymphomas are associated with a granulocytosis, but
no detectable lymphoid leukemia (25, 26). Lymphomatous $\mu$-myc animals, on the other hand, commonly show both a myelocytic leukemoid reaction and a substantial lymphoblastic leukemia. The granulocytosis might be provoked by factors released from the lymphoma cells.

Because there are many more large pre-B and B cells than normal in the spleen and bone marrow of the prelymphomatous $\mu$-myc mouse (14), it seemed likely that the B cells in the blood would also be larger. The average size of total leukocyte nuclei in young adult transgenic animals did tend to be higher than normal (Table IV and Fig. 4), but larger differences were seen with younger animals, most weanling transgenic and nontransgenic animals falling into two distinct groups (Fig. 5). We have subsequently used this rapid test to identify transgenic progeny in the $\mu$-myc line, with an error rate of <5% in several hundred mice. The apparent bimodal distribution of mean nuclear volumes among the transgenic weanlings (Fig. 5) may reflect their genetic heterogeneity and is under investigation. The blood cell assays revealed that, early in life, elevated numbers of enlarged lymphoid (presumably B or pre-B) cells circulate in the blood of the $\mu$-myc mouse. This phenomenon is present at 21 d through 33 d of age, but has almost disappeared by 42 d (Fig. 4). In a few animals, of course, the early leukocytosis reflects early-onset leukemia, but in the majority, whose tumors initiate later, there is an intervening period in which the size and number of blood white cells are near normal.

All $\mu$-myc tumors seem to derive from the B-lymphoid lineage, but they are not all uniform in phenotype; we found pre-B lymphomas, mixed pre-B and B lymphomas, and B lymphomas. The random initiation and the demonstrated clonality of $\mu$-myc tumors (16) indicate that the mixed tumors, and perhaps even the “pure” B lymphomas, are descendants of malignant pre-B cells that can differentiate. In this respect, they differ from Abelson tumors that rarely make the step from pre-B cell to surface Ig-expressing B cell (29, 30). We have seen no evidence of spontaneous plasmacytoma, the third main class of B-lineage tumor, by electrophoretic screening of many $\mu$-myc sera for paraproteins (Harris, A. W. and M. Crawford, unpublished observations).

We looked for possible relationships with the tumors that arise in some nontransgenic littermate animals possessing the same mixture of C57BL and SJL genes. None of more than 100 nontransgenic animals developed tumors within the first 9 mo of life, a period that saw 98% of the $\mu$-myc group succumb; but when monitoring was concluded at 18 mo, the incidence was 37%. The tumors, which enlarged some lymphoid organs, varied histologically from uniformly large lymphoid cells, through mixed collections of lymphoid and nonlymphoid cells, to sarcoma-like masses of fusiform cells. They were all readily distinguishable from the lymphoblastic lymphomas in the transgenic animals. Also, the lung infiltration was nodular rather than diffuse. Thus, the $\mu$-myc transgene did not simply hasten the onset of the tumors that would have occurred later in its absence.

The tumors in the nontransgenic animals resembled those characteristic of middle-aged SJL mice. SJL tumors vary in cell composition, and their classification, nature, and malignant character is uncertain (19, 21, 31–33). Some are said to contain neoplastic pre-B cells (31) and many are associated with clonal
proliferations of Ig-secreting cells (34). Therefore, despite the morphological differences between SJL and Eµ-myc tumors, SJL genes (such as Rcs-1 [35]) that predispose to the so-called reticulum cell neoplasm may accelerate lymphomagenesis in Eµ-myc animals. Our preliminary results with C57BL-backcross animals support this idea and suggest that the Eµ-myc strain might be useful in exploring other inbred mouse strains for genes which can modulate B-lymphoid tumorigenesis.

Because the initiation of malignancy occurs at random in Eµ-myc mice, we believe these mice constitute a model of spontaneous onset lymphoma and leukemia. In its high incidence early in life, rapid progression, mixed lymphoma-leukemia pathology and predominantly pre-B cell origin, the disease can be considered as a murine analog of the common form of childhood acute lymphoblastic leukemia (36–38). The nature of the low-frequency events, possibly spontaneous mutations in other oncogenes, that generate the first neoplastic lymphoid cell is under study. Such animals should provide a highly sensitive assay for carcinogens. Moreover, by introducing other known oncogenes into these animals, or into their pre-B cells in vitro, it should be feasible to delineate which of them can cooperate with a dysregulated myc gene to precipitate B-lymphoid malignancy.

Summary

Mice transgenic for a c-myc gene driven by the IgH enhancer (Eµ-myc) were shown to almost invariably develop lymphomas, 90% succumbing in the first 5 mo of life. The tumors typically presented as rapidly progressive lymphadenopathy with thymic involvement and were highly malignant by transplantation assay. Morphologically, they were lymphoblastic lymphomas, usually accompanied by lymphoid leukemia and granulocytosis, and were distinct from the tumors that arose much later in 37% of nontransgenic mice of the same (C57BL/6 × SJL)F₂ genetic background. Cell-surface markers on 31 Eµ-myc tumors identified 52% as pre-B lymphomas, 29% as mixed pre-B and B lymphomas, and 19% as B lymphomas. The tumors appeared to arise at random from a population of pre-B cells expanded by constitutive expression of the myc transgene. A majority of the animals initiated malignancy at the rate of 17% per week. The rate at which the cycling, benign pre-B cells spontaneously convert to malignancy was estimated to about $10^{-10}$ per cell per generation.

A transient leukocytosis identified in young Eµ-myc mice was developed into a rapid assay for inheritance of the transgene.

We thank Helen Abud, Tracey Watson, Craig Hyland, and Myrna Trumbauer for technical assistance; Drs. S. Cory, T. E. Mandel, and T. N. Fredrickson for discussions; Dr. F. Battye for setting up the Coulter Counter system and for assistance with flow cytometry; Warren Alexander and Leonie Gibson for tail blots; and Steven Mihajlovic and the late Alex Barberos for histologic processing.

Received for publication 5 October 1987.

References

1. Klein, G., and E. Klein. 1985. Myc/Ig juxtaposition by chromosomal translocations: some new insights, puzzles and paradoxes. Immunol. Today. 6:208.
LYMPHOMA AND LEUKEMIA IN Eu-myc MICE

2. Cory, S. 1986. Activation of cellular oncogenes in hemopoietic cells by chromosome translocations. Adv. Cancer Res. 47:189.
3. Kelly, K., and U. Siebenlist. 1986. The regulation and expression of c-myc in normal and malignant cells. Annu. Rev. Immunol. 4:317.
4. Cole, M. D. 1986. The myc oncogene: its role in transformation and differentiation. Annu. Rev. Genet. 20:361.
5. Studzinski, G. P., Z. S. Breit, S. C. Feldman, and R. A. Watt. 1986. Participation of c-myc protein in DNA synthesis of human cells. Science (Wash. DC). 234:467.
6. Iguchi-Ariga, S. M. M., T. Itani, Y. Kiji, and H. Ariga. 1987. Possible function of the c-myc product: promotion of cellular DNA replication. EMBO (Eur. Mol. Biol. Organ.). J. 6:2365.
7. Kelly, K., B. H. Cochran, C. D. Stiles, and P. Leder. 1983. Cell-specific regulation of the c-myc gene by lymphocyte mitogens and platelet-derived growth factor. Cell. 35:603.
8. Palmiter, R. D., and R. L. Brinster. 1986. Germ-line transformation of mice. Annu. Rev. Genet. 20:465.
9. Cory, S., and J. M. Adams. 1988. Transgenic mice and oncogenesis. Annu. Rev. Immunol. In press.
10. Stewart, T. A., P. K. Pattengale, and P. Leder. 1984. Spontaneous mammary adenocarcinomas in transgenic mice that carry and express MTV/myc fusion genes. Cell. 38:627.
11. Leder, A., P. K. Pattengale, A. Kuo, T. A. Stewart, and P. Leder. 1986. Consequences of widespread deregulation of the c-myc gene in transgenic mice: multiple neoplasms and normal development. Cell. 45:485.
12. Corcoran, L. M., S. Cory, and J. M. Adams. 1985. Transposition of the immunoglobulin heavy chain enhancer to the myc oncogene in a murine plasmacytoma. Cell. 40:71.
13. Alexander, W. S., J. W. Schrader, and J. M. Adams. 1987. Expression of the c-myc oncogene under control of an immunoglobulin enhancer in Eu-myc transgenic mice. Mol. Cell. Biol. 7:1436.
14. Langdon, W. Y., A. W. Harris, S. Cory, and J. M. Adams. 1986. The c-myc oncogene perturbs B lymphocyte development in Eu-myc transgenic mice. Cell. 47:11.
15. Vaux, D. L., J. M. Adams, W. S. Alexander, and B. L. Pike. 1987. Immunological competence of B cells subjected to constitutive c-myc oncogene expression in Eu-myc transgenic mice. J. Immunol. In press.
16. Adams, J. M., A. W. Harris, C. A. Pinkert, L. M. Corcoran, W. S. Alexander, S. Cory, R. D. Palmiter, and R. L. Brinster. 1985. The c-myc oncogene driven by immunoglobulin enhancers induces malignancy in transgenic mice. Nature (Lond.). 318:533.
17. Brinster, R. L., H. Y. Chen, M. Trumbauer, A. W. Senear, R. Warren, and R. D. Palmiter. 1981. Somatic expression of herpes thymidine kinase in mice following injection of a fusion gene into eggs. Cell. 27:223.
18. Brinster, R. L., H. Y. Chen, M. E. Trumbauer, M. K. Yagle, and R. D. Palmiter. 1985. Factors affecting the efficiency of introducing foreign DNA into mice by microinjecting eggs. Proc. Natl. Acad. Sci. USA. 82:4438.
19. Pattengale, P. K., and C. R. Taylor. 1983. Experimental models of lymphoproliferative disease. The mouse as a model for human non-Hodgkin's lymphomas and related leukemias. Am. J. Pathol. 113:237.
20. Murphy, E. D. 1983. SJL/J, a new inbred strain of mouse with a high, early incidence of reticulum-cell neoplasms. Proc. Am. Assoc. Cancer Res. 4:46.
21. Dunn, T. B., and M. K. Deringer. 1968. Reticulum cell neoplasm, type B, or the “Hodgkin’s-like lesion” of the mouse. *J. Natl. Cancer Inst.* 40:771.
22. McKenzie, I. F. C., and T. Potter. 1979. Murine lymphocyte surface antigens. *Adv. Immunol.* 27:179.
23. Pattengale, P. K., C. R. Taylor, P. Twomey, S. Hill, J. Jonasson, T. Beardsley, and M. Haas. 1982. Immunopathology of B-cell lymphomas induced in C57BL/6 mice by dualtropic murine leukemia virus. *Am. J. Pathol.* 107:362.
24. Strober, S., E. S. Gronowicz, M. R. Knapp, S. Slavin, E. S. Vitetta, R. A. Warnke, B. Kotzin, and J. Schröder. 1979. Immunobiology of a spontaneous B cell leukemia (BCL). *Immunol. Rev.* 48:169.
25. Abelson, H. T., and L. S. Rabstein. 1970. Lymphosarcoma: virus-induced thymic-independent disease in mice. *Cancer Res.* 30:2213.
26. Siegler, R., S. Zajdel, and J. Lane. 1972. Pathogenesis of Abelson-virus-induced murine leukemia. *J. Natl. Cancer Inst.* 48:189.
27. Opstelten, D., and D. G. Osmond. 1985. Regulation of pre-B cell proliferation in bone marrow: immunofluorescence stathmokinetic studies of cytoplasmic μ chain-bearing cells in anti-IgM-treated mice, hematologically deficient mutant mice and mice given sheep red blood cells. *Eur. J. Immunol.* 15:599.
28. Dunn, T. B., J. B. Moloney, A. W. Green, and B. Arnold. 1961. Pathogenesis of a virus-induced leukemia in mice. *J. Natl. Cancer Inst.* 26:189.
29. Alt, F., N. Rosenberg, S. Lewis, E. Thomas, and D. Baltimore. 1981. Organization and reorganization of immunoglobulin genes in A-MuLV-transformed cells: rearrangement of heavy but not light chain genes. *Cell.* 27:381.
30. Sugiyama, H., S. Akira, N. Yoshida, S. Kishimoto, Y. Yamamura, P. Kincade, T. Honjo, and T. Kishimoto. 1982. Relationship between the rearrangement of immunoglobulin genes, the appearance of a B lymphocyte antigen and immunoglobulin synthesis in murine pre-B cell lines. *J. Immunol.* 126:2793.
31. Ford, R. J., B. Ruppert, and A. L. Maizel. 1981. SJL tumor: a neoplasm involving macrophages. *Lab. Invest.* 45:11.
32. Bonavida, B. 1983. SJL/J spontaneous reticulum cell sarcoma: new insights in the fields of neoantigens, host-tumor interactions, and regulation of tumor growth. *Adv. Cancer Res.* 38:1.
33. Brown, P. H., and G. J. Thorbecke. 1985. Characterization of the molecules on SJL/J lymphomas which stimulate syngeneic T cells. *J. Immunol.* 135:3572.
34. McIntire, K. R., and L. W. Law. 1967. Abnormal serum immunoglobulins occurring with reticular neoplasms in an inbred strain of mouse. *J. Natl. Cancer Inst.* 39:1197.
35. Bubbers, J. E. 1984. Identification and linkage analysis of a gene, Rcs-1, suppressing spontaneous SJL/J lymphoma expression. *J. Natl. Cancer Inst.* 72:441.
36. Lennert, K. 1978. Malignant Lymphomas. Springer-Verlag, Berlin. 402–421.
37. Greaves, M. F. 1986. Differentiation-linked leukemogenesis in lymphocytes. *Science (Wash. DC).* 234:697.
38. Greaves, M. F., and L. C. Chan. 1986. Is spontaneous mutation the major cause of childhood acute lymphoblastic leukemia? *Br. J. Haematol.* 64:1.
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
HARRIS, AW; PINKERT, CA; CRAWFORD, M; LANGDON, WY; BRINSTER, RL; ADAMS, JM

Title:
THE E-MU-MYC TRANSGENIC MOUSE - A MODEL FOR HIGH-INCIDENCE SPONTANEOUS LYMPHOMA AND LEUKEMIA OF EARLY B-CELLS

Date:
1988-02-01

Citation:
HARRIS, A. W., PINKERT, C. A., CRAWFORD, M., LANGDON, W. Y., BRINSTER, R. L. & ADAMS, J. M. (1988). THE E-MU-MYC TRANSGENIC MOUSE - A MODEL FOR HIGH-INCIDENCE SPONTANEOUS LYMPHOMA AND LEUKEMIA OF EARLY B-CELLS. JOURNAL OF EXPERIMENTAL MEDICINE, 167 (2), pp.353-371. https://doi.org/10.1084/jem.167.2.353.

Persistent Link:
http://hdl.handle.net/11343/258429

File Description:
Published version

License:
CC BY-NC-SA