

HIGH RESOLUTION BANDING ANALYSIS OF THE
INVOLVEMENT OF STRAIN BALB/C- AND AKR-
DERIVED CHROMOSOMES NO. 15 IN PLASMACYTOMA-
SPECIFIC TRANSLOCATIONS

BY FRANCIS WIENER,* MAGDA BABONITS,* URSULA BREGULA,*
GEORGE KLEIN,* ALAIN LÉONARD,† JUDITH S. WAX,‡ AND
MICHAEL POTTER§

*From the *Department of Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden; †Laboratoire du C E N, B-2400 MOL, Belgium; ‡Laboratory of Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

Our previous cytogenetic studies on murine T cell leukemias and plasmacytomas have suggested that gene(s) located in the distal segment of chromosome 15 are involved in the genesis of these malignancies (1–5). This segment tended to duplicate during T cell leukemogenesis, whereas in plasmacytomas it was transposed to chromosome 12 or 6 (6, 7), known to carry the Ig heavy chain and the kappa light chain locus, respectively (8).

Leukemias induced in heterozygous F₁ mice with cytogenetically distinguishable chromosomes No. 15 showed an asymmetry of the leukemia-associated duplication pattern; i.e., one of the two parental 15 chromosomes was preferentially duplicated (9–11). This preference showed a consistent “hierarchy” between different mouse strains. Since the two complementary products of nondisjunction are generated with the same frequency, the likelihood of leukemia development must be different, depending on the strain derivation of the duplicated 15 chromosome. We have taken this to suggest that the gene involved in leukemia development, or its regulatory element, is subject to genetic variation.

On the basis of these cytogenetic studies, we have suggested that the segment of chromosome 15 distal to band D2/3 carries an oncogene that plays an essential role in the genesis of these tumors. Viral promoter insertion and/or regulation mutation appeared as the more likely mechanisms of oncogene activation for the T cell lymphomas. The chromosome that carried the activated gene would need to be duplicated to overcome a *trans*-acting regulatory influence emanating from the normal homologue. Somatic hybrid studies gave positive evidence for a *trans*-acting control of this type (12).

We have also suggested that the activation of the same oncogene is responsible for the genesis of the murine plasmacytomas (7). Transposition of the same chromosome segment to a functionally active Ig gene region would lead to the

Supported by U. S. Public Health Service grant number 2 R01 CA 25250-03, awarded by the National Cancer Institute and by the Swedish Cancer Society. U. B. is on leave from the Institute of Oncology, Warsaw, Poland.

switch of the oncogene in this cell (13).

Recent molecular studies confirmed some of these ideas (reviewed in reference 14). They showed that a cellular oncogene, *c-myc*, is localized on the distal segment of chromosome 15, in the immediate vicinity of the translocation breakpoint. In the plasmacytomas, it is transposed into the Ig gene area. In the majority of the 12;15 translocations so far studied, *c-myc* was found to rearrange to the S region of the IgH gene.

Plasmacytomas are highly differentiated B cell tumors that can be readily induced in BALB/c and NZB mice (15, 16). The specific t(12;15) and rcpt(6;15) translocation chromosomes are regularly present, irrespectively of the mode of induction. Unrelated mouse strains and various BALB/c F₁ outcross hybrids are usually much less susceptible to plasmacytoma induction.

In the present study, we have asked the question whether the high susceptibility of the BALB/c strain to plasmacytoma induction is linked to some peculiarity of the *c-myc*-carrying region of chromosome 15. If so, one might expect that plasmacytomas induced in F₁ hybrids derived from the cross of BALB/c with a more resistant strain would show a preferential transposition of the distal segment of the BALB/c-derived chromosome 15 to chromosome 12 or 6, in comparison with the corresponding chromosome segment derived from the more resistant strain. This was examined for the AKR(6;15) × BALB/c cross where the chromosomes 15 of the two parental strains could be cytogenetically distinguished. We found no significant preference for the BALB/c-derived chromosome 15 although it served somewhat more frequently as the donor of the transposed segment than its AKR-derived counterpart. As a byproduct, we have discovered three tumors where the plasmacytoma-associated variant 6;15 translocation arose by the pericentric inversion of the AKR-derived Robertsonian 6;15 chromosome, i.e., by an exchange within a single chromosomal element.

Materials and Methods

AKR(6;15) Mice. The Rb(6;15) 1 Ald translocation was observed in 1966, in a small inbreeding stock of AKR mice (17). This strain of mice is syngeneic to the AKR/J (The Jackson Laboratory, Bar Harbor, ME) from which it originated in 1961.

Plasmacytoma Induction. AKR(6;15) mice were crossed with BALB/c to produce an F₂ population. Spleen or peripheral blood lymphocytes from these mice were cultured and examined cytologically for Rb 6;15 chromosomes. One male carrying Rb 6;15/Rb 6;15 was identified and mated to BALB/c females to raise a backcross population of the genetic constitution Rb 6;15/6;15. Plasmacytomas were induced in these mice by three i.p. injections of 0.5 ml pristane (2,6,10,14-tetramethyl pentadecane; Aldrich Chemical Co., Milwaukee, WI).

Of 60 mice, 28 developed plasmacytomas in the first year. Morphologically, the tumors were typical plasmacytomas and were transplanted to pristane-conditioned (BALB/c × AKR 6;15)F₁ mice. The heavy chain classes of these tumors secrete IgG and IgA type myeloma proteins. The tumors were cytologically typed in the original mouse or in the first generation transplant recipient.

Chromosome Preparation. Metaphase plates were prepared from the ascitic form of the plasmacytomas, without colcemid treatment. Banding was performed by a slight modification of Wang and Fedoroff's method (18). Chromosomes were identified according to the Standard Mouse Karyotype (19).

Breakpoint Analysis. Breakpoints were determined by high resolution banding according to the method of Rybak et al. (20). Sub-band localization followed the nomenclature of Nesbitt and Francke (21).

Results

Table I summarizes the passage history, chromosome constitution, and translocation type of the plasmacytomas analyzed. Table II shows the results of the G-banding analysis. A total of 101 plates were karyotyped and analyzed, 7–12 plates per tumor. Possible alternatives are illustrated schematically in Fig. 1, A–E. We have actually found six tumors that carried translocations corresponding to alternative A, one with B, none with C or D, and three with an originally unexpected pericentric inversion, included in Fig. 1 as alternative E. Back to our original question, as far as the strain derivation of chromosome 15 is concerned, this means that the tumors fall into the following two groups: (a) The six plasmacytomas that behaved according to alternative A contained the typical t(12;15) translocation, with the BALB/c-derived chromosome 15 as the donor of the transposed segment (Fig. 2). (b) In the four remaining plasmacytomas CAKTepc 2002 (alternative B), CAKTepc 1198, 1199, and 2014 (alternative E), the distal part of the AKR-derived chromosome 15 (part of the Robertsonian 6;15 fusion chromosome) was translocated. In CAKTepc 2002, it moved to chromosome 12 (Fig. 3), generating a typical t(12;15) translocation. CAKTepc

TABLE I
Passage History, Chromosome Constitution, and Translocation Pattern of the Plasmacytomas Induced in (BALB/c × AKR 6;15) × BALB/c Backcross Mice

Plasmacytoma	Passage generation	Modal chromosome no.	No. of karyotyped plates	Type of translocation	Alternative in Fig. 1
CAKTEPC 1192	2	58	7	t(12;15)	A
1198	6	49	11	inv(Rb 6;15)	E
1199	4	72	11	inv(Rb 6;15)	E
2000	6	80	12	t(12;15)	A
2002	5	72	10	t(12;15)	B
2003	5	74	9	t(12;15)	A
2004	2	65	7	t(12;15)	A
2005	3	91	10	t(12;15)	A
2006	2	71	12	t(12;15)	A
2014	6	68	12	inv(Rb 6;15)	E

TABLE II
Mean Chromosome Number per Total Analyzed Plates

Tumor	Transplant generation	No. of plates	Chromosome													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
CAKTepc 1192	2	7	3.0	3.2	3.2	3.2	3.0	2.0	2.8	2.2	3.2	3.0	3.2	1.2	1.8	1.8
CAKTepc 1198	6	11	2.5	2.4	2.5	1.6	2.5	1.3	2.3	2.5	2.5	2.5	2.5	2.5	2.4	2.5
CAKTepc 1199	4	11	4.2	3.6	4.2	4.1	3.8	2.0	3.4	3.5	2.9	4.1	3.4	1.9	3.1	0.9
CAKTepc 2000	6	12	3.8	4.3	4.0	4.0	3.0	2.0	3.8	3.0	3.9	3.8	3.1	1.9	3.7	3.3
CAKTepc 2002	5	10	5.6	4.0	4.0	4.0	4.0	4.0	3.6	3.0	4.0	4.0	5.3	2.0	3.6	3.3
CAKTepc 2003	5	9	3.7	3.7	3.8	3.1	3.2	2.0	3.3	3.1	3.6	4.0	4.4	1.8	3.5	3.8
CAKTepc 2004	2	7	4.7	3.8	4.0	4.0	3.1	2.0	3.4	3.7	4.0	4.0	4.5	2.0	3.2	3.0
CAKTepc 2005	3	10	4.0	3.0	3.5	3.7	3.0	1.7	3.2	3.2	3.2	3.0	4.5	1.5	3.2	2.7
CAKTepc 2006	2	12	5.8	4.8	4.0	3.8	3.8	2.0	3.9	3.9	4.0	4.9	4.9	1.9	4.0	3.8
CAKTepc 2014	6	12	3.9	3.2	4.0	4.0	4.0	2.0	3.7	3.2	2.4	3.7	4.1	2.1	2.3	0.5

1198, 1199, and 2014 showed a very different and previously unidentified pattern. A variant translocation of the *rcpt(6;15)* type was generated by two breaks in the single AKR-derived Rb 6;15 chromosome, with pericentric inversion as the result (Fig. 4). Since this extraordinary reciprocal translocation that affected the two distal ends of a single Robertsonian chromosome appeared in three different tumors, contamination had to be excluded. This was readily achieved by the detailed cytogenetic analysis. As shown in Table II, CAKTepc 1198 has a marker chromosome in all plates analyzed. One of the chromosomes No. 4 was elongated, possibly due to an interstitial duplication (Fig. 4). In CAKTepc 1199 this marker chromosome was absent; this tumor contained

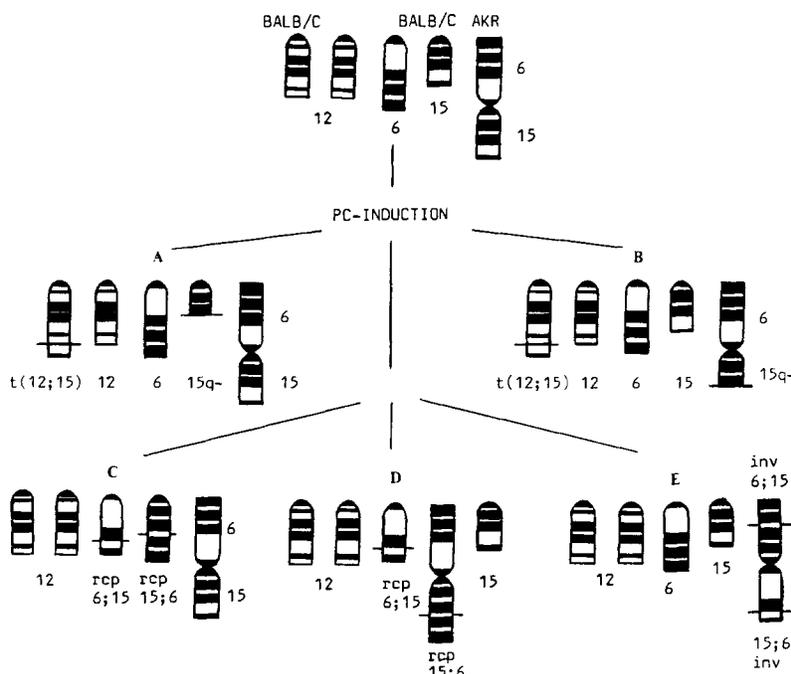


FIGURE 1. Chromosome constitution of normal mouse derived from the (BALB/c × AKR 6;15) × BALB/c backcross (top row). Possible translocation patterns of plasmacytomas induced in (BALB/c × AKR 6;15) × BALB/c backcross mice.

numbers															
15	16	17	18	19	X	Rb 6;15	6;15q-	Inv. 6;15	12q+	15q-	14q-	4q+	Marker Chr.	Rb 11;11	Total Chr. No.
1.0	3.0	2.6	2.8	2.8	2.8	1.4			1.8	1.4			1.0		58.2
1.2	2.4	2.5	2.3	2.5	2.5			1.3							49.0
2.0	3.7	4.1	3.7	4.0	2.9			2.0				0.9		0.7	72.2
0.0	3.6	3.7	4.0	3.3	2.1	2.0			2.0	2.0			1.0		71.1
2.0	4.6	3.6	4.0	3.6	3.3	1.0	1.0		2.0				1.0		80.0
0.5	3.7	3.6	3.6	3.4	3.7	1.8			2.0	2.0			0.8		72.0
0.0	4.7	3.4	3.8	3.1	3.8	2.0			2.0	2.0					74.0
0.2	3.0	3.0	2.5	3.0	3.2	2.0			2.5	1.25					64.5
0.0	4.7	2.9	3.9	3.8	3.9	2.0			2.9	1.9					91.0
1.9	4.0	3.4	3.3	3.8	2.1			1.9	2.0		1.9		0.8		68.2

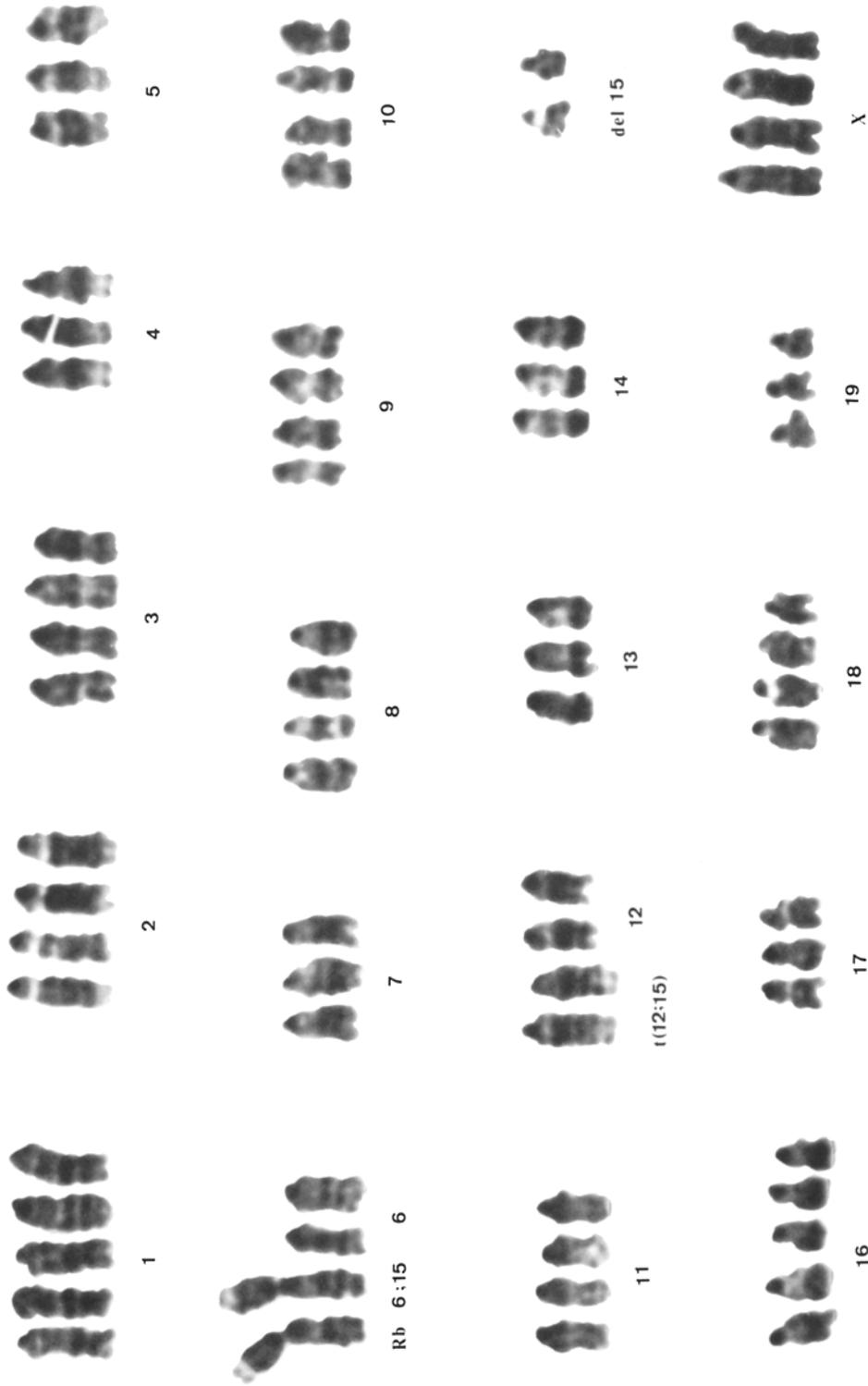


FIGURE 2. G-banded karyotype of a hypotetraploid plasmacytoma. CAK-15 translocated onto chromosome 12. The AKR-derived Rb 6;15 chromosomes are present in two copies (corresponds to alternative A of Fig. 1).

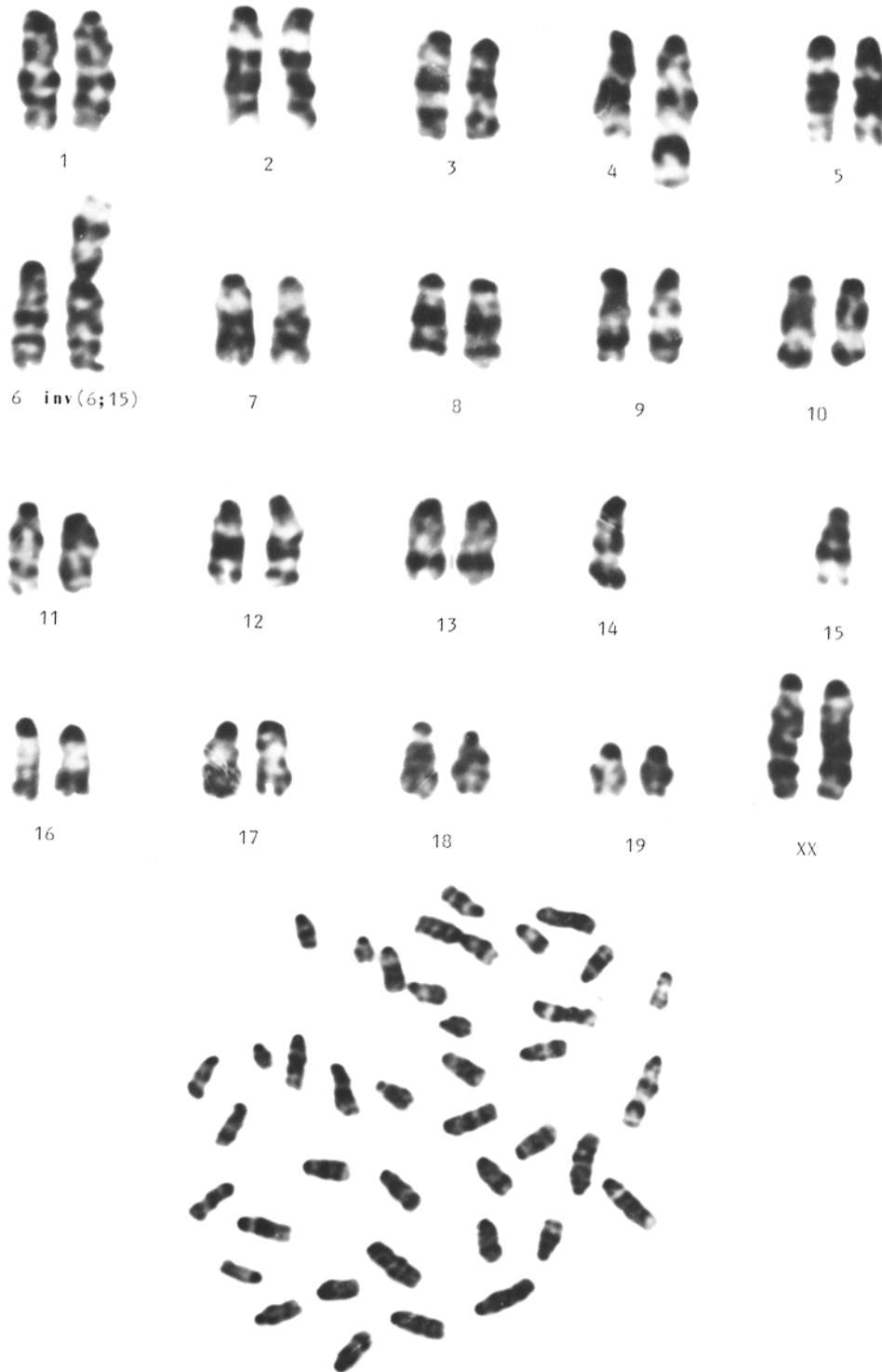
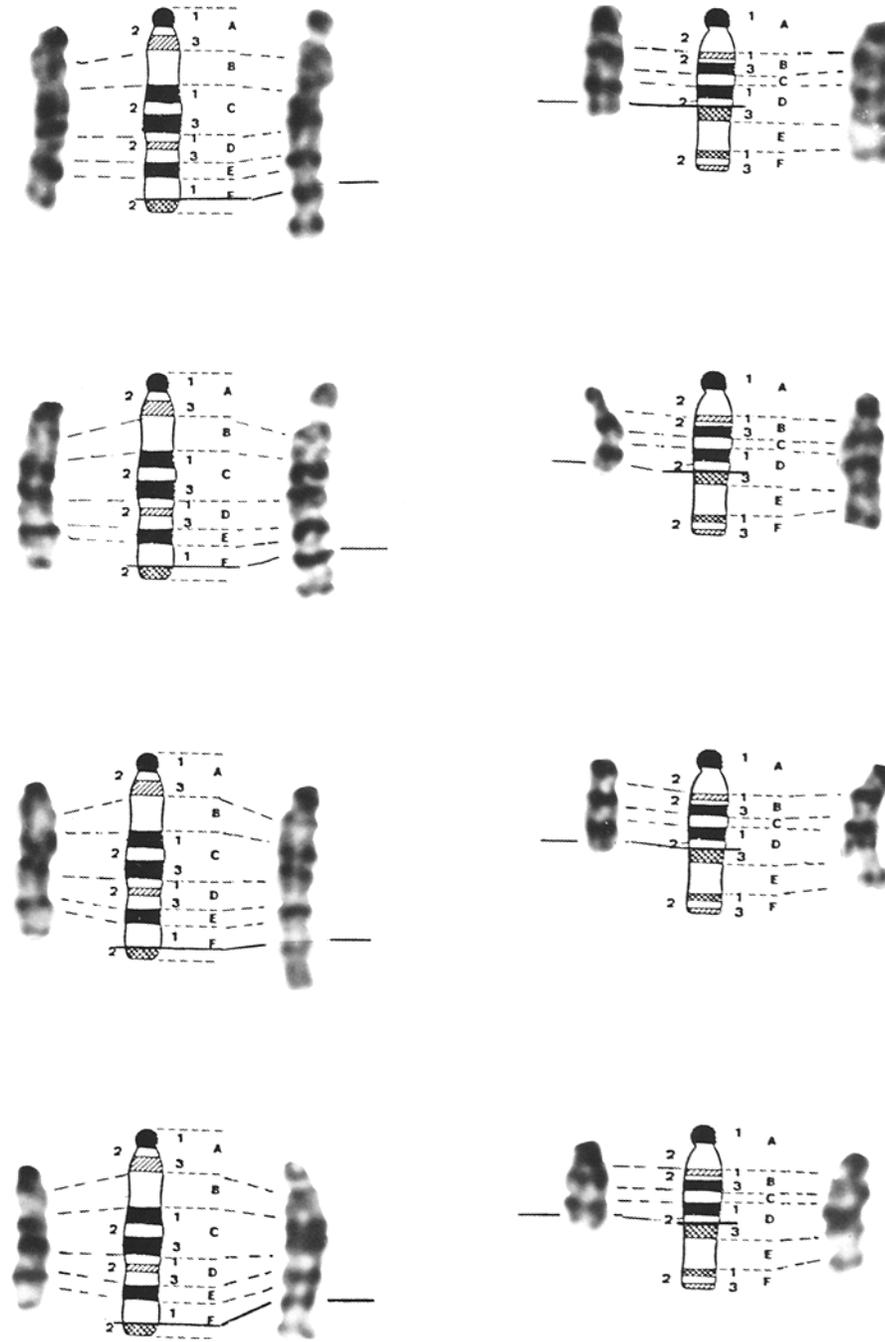


FIGURE 4. G-banded karyotype of the near-diploid plasmacytoma CAKTepc 1198. The AKR-derived Rb 6;15 chromosome has undergone pericentric inversion, leading to an $rept(6;15)$ translocation (details in Fig. 7). The BALB/c-derived chromosomes 6 and 15 are intact (corresponds to alternative *E* of Fig. 1). Note the interstitial duplication in one of chromosome 4.



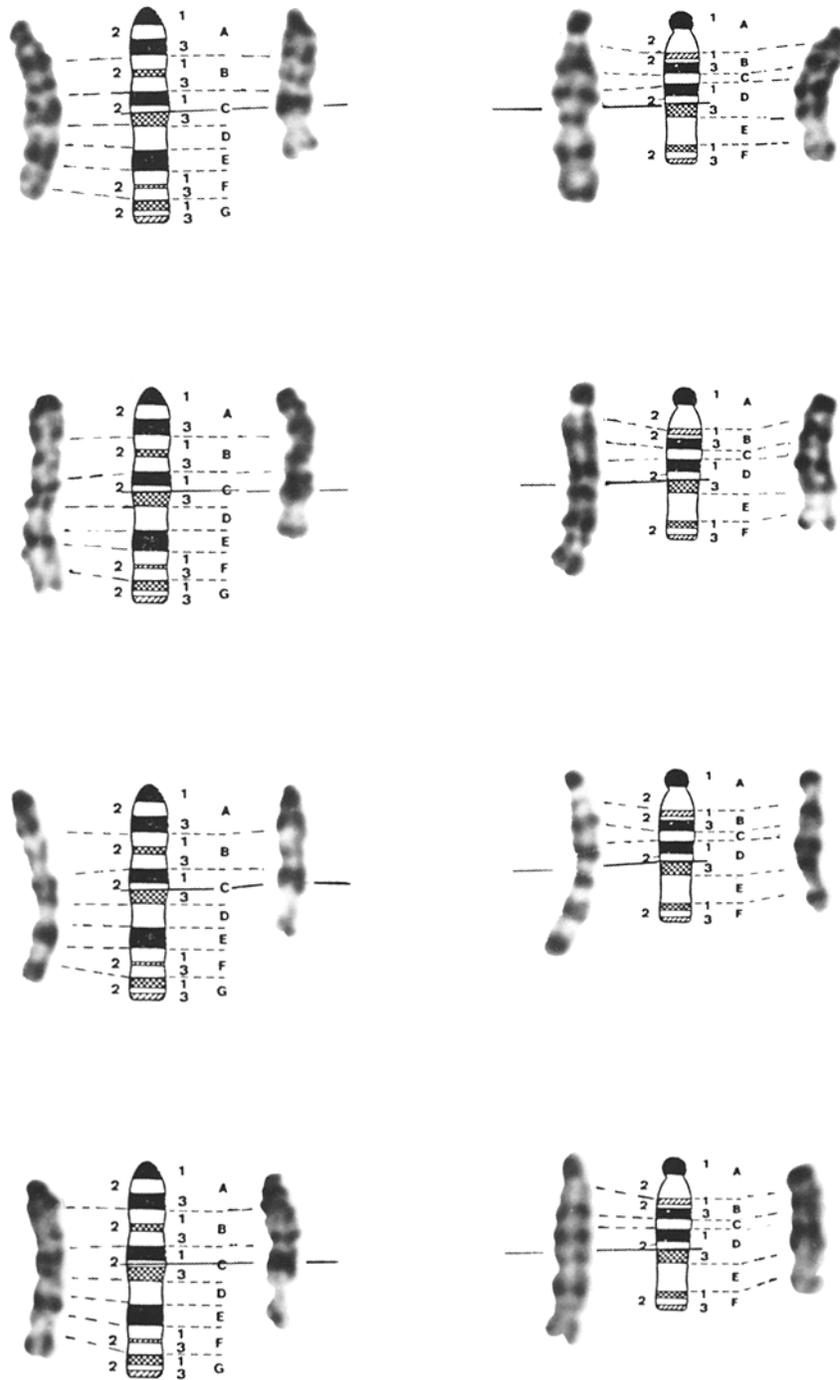
12

rcpt(12;15)

rcpt(15;12)

15

FIGURE 5. High resolution banding of the chromosomes involved in a t(12;15) translocation. Note that the F₂ band of chromosome 12 is translocated onto the band D2/3 of chromosome 15. The breakpoint affects band F₁ on chromosome 12. The translocation is reciprocal.



6 **rcpt(6;15)** **rcpt(15;6)** 15
 FIGURE 6. High resolution banding of the chromosomes involved in the $rcpt(6;15)$ translocation in plasmacytomas ABPC-4 (Ohno et al., submitted for publication). The breakpoints are at D2/3 on chromosome 15 and C2 on chromosome 6.



FIGURE 7. High resolution banding of the $rcp(6;15)$ translocation generated by the pericentric inversion of the AKR-derived $Rb(6;15)$ chromosome in CAKTe_pc 1198 plasmacytoma. This translocation arose by two breaks of the chromosome arms on each side of the centromere. Note the identity of the breakpoints with those involved in the usual $rcp(6;15)$ translocation (Fig. 6).

another marker, generated by a translocation between chromosomes 12 and 14, i.e., t(12;14). Interestingly enough, in CAKTepc 2014 both inv(Rb, 6;15) and the t(12;14) chromosomes were present, similarly to those found in CAKTepc 1199.

Breakpoint Analysis. In our previous studies (6, 7) we have attempted to define the breakpoints on chromosomes 6, 12, and 15 by conventional G-banding. The limits of the technique did not permit an accurate definition, however. It was also unclear whether the t(12;15) rearrangement was reciprocal or of the deletion type. By using a high resolution banding (HRB) technique we could now settle this issue and determine the breakpoints more exactly.

The HRB analysis confirmed the reciprocal nature of the t(12;15) translocation. The breakpoint was located between bands D2 and D3 (D2/3) on chromosome 15 and within band F₁ on chromosome 12. The F₂ band of chromosome 12 was translocated onto D2/3 of chromosome 15 (Fig. 5). The rearrangement should be designated as rcpt(12;15).

The breakpoints on the rcpt(6;15) translocation were presently analyzed in the plasmacytoma ABPC-4 (Ohno, S., S. Migita, F. Wiener, M. Babonits, G. Klein, F. Mushinski, and M. Potter. Cytogenetic studies on plasmacytomas induced in BALB/c mice by pristane and Abelson virus. Submitted for publication) in order to facilitate comparison with the pericentric inversion observed in the CAKTepc 1198, 1199, and 2014 tumors of the present series. HRB analysis confirmed our previous conclusion from conventional G-banding. The breakpoint on chromosome 15 was within bands D2/3 and on chromosome 6 in band C2 (Fig. 6).

HRB analysis of the inv (Rb 6;15) chromosomes in tumors CAKTepc 1198, 1199, and 2014 was of particularly great interest. It showed that the breakpoints were the same as in the usual rcpt(6;15) that arises by a reciprocal exchange between two independent chromosomes, namely bands D2/3 on chromosome 15 and C2 on chromosome 6 (Fig. 7).

Discussion

Chromosome 15 is regularly involved in the nonrandom chromosomal changes that occur most frequently in murine T cell lymphomas and in plasmacytomas. Trisomy, due to the duplication of one chromosome 15 is the most regular and often the single chromosome change seen in the T cell lymphomas, irrespective of their mode of induction (22). Studies on mice with reciprocal translocations have shown that the important segment that tends to become duplicated in the course of leukemogenesis is localized in the distal part of chromosome 15 (3, 5). In plasmacytomas, the same distal segment is translocated to the Ig heavy chain locus carrying chromosome 12 or to the kappa gene-carrying chromosome 6 (6, 7).

AKR mice develop spontaneous T cell leukemias with great frequency. Several genes contribute to this process, including two or more integrated ecotropic proviral genes Akv-1 and 2, a viral amplification gene (Fv-1), and a gene that renders the mice immunologically unresponsive to the leukemic cells (Rgv-1^s). In addition, AKR mice also carry gene(s) that increase the likelihood of the

neoplastic transformation at the level of the target T cell itself.

We have previously found that the AKR-derived chromosome 15 duplicates preferentially in trisomic leukemias induced in F₁ hybrid mice, to the complete exclusion of the chromosome 15 of the other genetically unrelated parent (9–11). Since the frequency of the two complementary trisomic types generated by nondisjunction must be equal, this must mean that the duplication of the AKR-derived chromosome 15 renders the target T cell more leukemia-prone than does the duplication of its partner.

The BALB/c strain has an extraordinary susceptibility to plasmacytoma induction by the intraperitoneal administration of mineral oil or by other means (15, 16). The BALB/c genes and gene products responsible for the susceptibility are presently unknown. Since the distal region of chromosome 15 is involved in plasmacytoma genesis, we wanted to examine the question whether the plasmacytoma-associated 12;15 or 6;15 translocation would preferentially use the BALB/c-derived chromosome No. 15, when in competition with chromosome 15 from another, plasmacytoma-resistant strain. When AKR mice are injected with pristane, most animals develop thymic leukemias, preventing a direct assessment of their plasmacytoma susceptibility. (BALB/c × AKR)F₁ mice appear to be resistant to plasmacytoma development, however (M. Potter and J. S. Wax, unpublished observations).

As a first step towards a more extensive study, we have introduced the AKR-derived chromosome No. 15 onto the background of the BALB/c strain. We could exploit the availability of a Robertsonian 6;15 fusion chromosome that has arisen in the AKR strain (17) and is easily distinguishable from the normal 15 chromosome of BALB/c.

The cytogenetic analysis of 10 tumors induced in backcross mice heterozygous for the AKR-derived 6;15 and the BALB/c-derived 15 chromosome have identified the BALB/c chromosome as the translocation donor in six of the tumors, whereas the AKR-derived 15 chromosome served in the same capacity in the remaining four. Although larger numbers of tumors need to be examined, this material already indicates that chromosome 15 originating from these two strains participate in the tumor-associated translocation at random. This conclusion is further supported by our current experiments on another cross, where the CBA T6T6-derived t(14;15) chromosome was introduced on BALB/c background. CBA T6T6 and (BALB/c × CBA T6T6)F₁ mice are resistant to developing plasmacytomas (M. Potter and J. S. Wax, unpublished observations). So far, we have examined two plasmacytomas induced in the t(14;15) mice with a largely BALB/c background. Both carried the typical 12;15 translocation. It arose by the transposition of the distal segment of the CBA T6T6-derived 14;15 chromosome in both cases.

The lack of any demonstrable strain preference in the plasmacytoma-associated translocation, in contrast to the duplication asymmetry observed in the course of T cell leukemogenesis suggests that different mechanisms may be responsible for the development of these tumors. In plasmacytomas, the oncogene *c-myc*, localized at the translocation breakpoint on chromosome 15, was shown to rearrange to the immediate vicinity of an Ig locus (23–26). In plasmacytomas carrying the typical 12;15 translocation, the rearrangement is often (but not

always) to the S alpha region of the IgH complex. This insertion of *c-myc* into a functionally active chromosome region and/or the scission of its 5' end, presumed to carry regulatory elements of the gene, has been thought of as being responsible for the activation and/or abnormal transcription of the oncogene and subsequent neoplastic development (27).

If this is the correct scenario, it must also follow that the homologous unchanged chromosomes Nos. 15 and 12 do not exert any regulatory or suppressive influence on the expression of the tumorigenic phenotype. Unlike the T cell leukemia system, there is no chromosome amplification (trisomy). In the near-diploid plasmacytomas, the translocation chromosome and its normal homologue are present in a single copy each. In tetraploid plasmacytomas the ratio is 2:2, suggesting that the translocation occurs before the tetraploidization of the tumor. Since the primary tumor is already often tetraploid, this further supports our view that the translocation occurs in direct relationship to the tumorigenic event. This is also in line with the fact that the translocations are already found in primary (0 generation) tumors.

In the 15-trisomic T cell leukemias the situation is quite different. The very fact that only one of the two chromosomes No. 15 needs to be duplicated during leukemogenesis suggests an interplay between a changed gene and its regulators on the unchanged chromosome. We have previously suggested (22) that the function of the 15 duplication is to overcome its regulation either by a dosage effect at the gene or transcript level, or at the level of the protein product. Somatic hybrid studies have given experimental evidence confirming the existence of the postulated *trans*-acting control, by showing the regular amplification of the AKR leukemia-derived chromosome 15 and a concomitant decrease in the number of its normal CBA fibroblasts-derived homologues, in high tumorigenic but not in low tumorigenic hybrids (12). The duplication preference of the AKR-derived 15 chromosome in the trisomic F₁ hybrid leukemias—and the lack of a similar preference in the plasmacytoma system—may be understood against this background. If the presumed oncogene is activated by proviral promoter insertion or by regular mutation during T cell leukemogenesis, the likelihood of this event may differ greatly for 15-chromosomes different strains; selection of the AKR mouse for high leukemia incidence may have greatly increased its probability. In contrast, plasmacytomagenesis brings the *c-myc* oncogene under the direct influence of a highly active chromosome region. It is likely that the oncogene is activated constitutively by the *cis*-acting influence of an enhancer or a cryptic promoter in which case the strain origin of the oncogene itself may not matter.

It is also conceivable that BALB/c mice carry a non-chromosome 15-associated gene whose product may increase the likelihood of chromosome translocations, whereas the corresponding AKR gene would not have such an effect. Hence, there would be no strain difference between the 15 chromosomes of different origins, even though the two strains might differ by a non-chromosome 15-linked gene that could account for the difference in their plasmacytoma susceptibility.

A number of other findings have been made in the course of this study that deserve special mention. The apparently identical chromosome change observed

in the CAKTEpc 1198, 1199, and 2014 plasmacytomas is particularly noteworthy. In all three tumors, the AKR-derived Robertsonian (6;15) fusion chromosome has been solely responsible for the plasmacytoma-associated reciprocal translocation by exchanging its two terminal segments. The biamed chromosome has undergone a pericentric inversion, leading to the same type of transposition and with the same breakpoints as previously observed in the "variant" BALB/c plasmacytomas where two separate, normal 6 and 15 chromosomes participated in the exchange. The fact that this can occur even in a situation where the two chromosomes are fused with each other gives added weight to the importance of the translocations for plasmacytomagenesis.

Summary

Plasmacytomas were induced in (BALB/c \times AKR 6;15) \times BALB/c backcross mice where one of the BALB/c-derived chromosomes No. 15 was replaced by the AKR(6;15)-derived Robertsonian 6;15 chromosome. (BALB/c \times AKR 6;15) F_2 mice that were homozygous for Rb 6;15 were mated to BALB/c mice. Plasmacytomas were induced in the progeny by intraperitoneal injection of pristane. The cytogenetic marker permitted the distinctive identification of the two chromosome 15 homologues, including the distal segment involved in the plasmacytoma-specific translocations. 7 of the 10 plasmacytomas contained the typical t(12;15) translocation. The BALB/c-derived 15 chromosome served as the donor of the translocated segment in six of them. In the seventh, the Rb 6;15 chromosome of the AKR strain was the donor. The remaining three tumors contained the same type of intrachromosomal rearrangement. It arose by the pericentric inversion of the Rb 6;15 chromosome, leading to a variant plasmacytoma-associated rcpt(6;15) translocation. Unlike the usual 6;15 variant that arises by a reciprocal exchange between two separate chromosomes, it was generated by an exchange of the distal segments of a single chromosomal element. High resolution banding analysis of the tumors showed that all translocated breakpoints on chromosomes 15, 12, and 6 were identical with the previously described breakpoints characteristic for the typical 12;15 and the variant 6;15 translocation in murine plasmacytomas.

It is known that the distal segment of chromosome 15 carries the *c-myc* oncogene (23). The PC-associated translocations cut across the 5'-exon of *c-myc* in the majority of the cases (24, 26). The severed oncogene is transposed to the Ig-region on the recipient chromosome. Since the BALB/c strain is highly sensitive to PC-induction, we were interested to examine the question whether its chromosome 15 is preferred as the oncogene donor in AKR \times BALB/c backcross mice that carry cytogenetically distinguishable 15 chromosomes. Our results show that this is not the case, since the same segment of the AKR-derived chromosome 15 could also serve in the same capacity. This is in contrast with T cell leukemogenesis where we have previously found that the trisomization-associated duplication of chromosome 15 occurred in a highly asymmetrical fashion, depending on the donor strain of No. 15 (9-11).

References

1. Wiener, F., S. Ohno, J. Spira, N. Haran-Ghera, and G. Klein. 1978. Chromosomal changes (trisomy 15 and 17) associated with tumor progression in leukemias induced by radiation leukemia virus (RadLV). *J. Natl. Cancer Inst.* 61:227.
2. Wiener, F., J. Spira, S. Ohno, N. Haran-Ghera, and G. Klein. 1978. Chromosome changes (trisomy 15) in murine T-cell leukemia induced by 7,12-Dimethylbenz(a)anthracene (DMBA). *Int. J. Cancer.* 22:447.
3. Wiener, F., S. Ohno, J. Spira, N. Haran-Ghera, and G. Klein. 1978. Cytogenetic mapping of the trisomic segment of chromosome 15 in murine T-cell leukemia. *Nature (Lond.)*. 275:658.
4. Spira, J., F. Wiener, S. Ohno, and G. Klein. 1979. Is trisomy a cause or consequence of murine T-cell leukemia development? Studies on Robertsonian translocation mice. *Proc. Natl. Acad. Sci. USA.* 76:6619.
5. Spira, J., M. Babonits, F. Wiener, S. Ohno, Z. Wirschubsky, N. Haran-Ghera, and G. Klein. 1980. Non-random chromosomal changes in Thy-1 positive and Thy-1 negative lymphomas induced by 7,12-dimethylbenzanthracene (DMBA) in SJL mice. *Cancer Res.* 40:2609.
6. Ohno, S., M. Babonits, F. Wiener, J. Spira, G. Klein, and M. Potter. 1979. Non-random chromosome changes involving Ig-gene chromosomes (Nos. 12 and 6) in pristane induced mouse plasmacytomas. *Cell.* 18:1001.
7. Wiener, F., M. Babonits, J. Spira, G. Klein, and M. Potter. 1980. Cytogenetic studies on the IgA/lambda producing murine plasmacytomas. Regular occurrence of a t(12;15) translocation. *Somatic Cell Genet.* 6:731.
8. Hengartner, H., T. Meo, and E. Müller. 1978. Assignment of genes for immunoglobulin k and heavy chains to chromosomes 6 and 12 in mouse. *Proc. Natl. Acad. Sci. USA.* 75:4494.
9. Wiener, G., J. Spira, S. Ohno, N. Haran-Ghera, and G. Klein. 1979. Non-random duplication of chromosome 15 in murine T-cell leukemias induced in mice heterozygous for translocation T(14;15)6. *Int. J. Cancer.* 23:504.
10. Wiener, F., J. Spira, M. Babonits, N. Haran-Ghera, and G. Klein. 1980. Non-random duplication of chromosome 15 in murine T-cell leukemias. Further studies on translocation heterozygotes. *Int. J. Cancer.* 26:661.
11. Wiener, F., J. Spira, M. Babonits, and G. Klein. 1982. Non-random duplication of chromosome 15 in T-cell leukemias induced in mice heterozygous for reciprocal and Robertsonian translocations. *Int. J. Cancer.* 30:497.
12. Spira, J., F. Wiener, M. Babonits, J. Gamble, J. Miller, and G. Klein. 1981. The role of chromosome 15 in murine leukemogenesis. I. Contrasting behavior of the tumor vs. normal parent-derived chromosome No. 15 in somatic hybrids of varying tumorigenicity. *Int. J. Cancer.* 28:785.
13. Klein, G. 1981. The role of gene dosage and genetic transposition in carcinogenesis. *Nature (Lond.)*. 294:313.
14. Potter, M., F. Mushinski, and F. Wiener. Recent developments in plasmacytoma genesis in mice. *Adv. Viral. Oncology*. In press.
15. Potter, M. 1972. Immunoglobulin-producing tumors and myeloma proteins in mice. *Physiol. Rev.* 52:631.
16. Morse, H. C. III, J. W. Hartley, and M. Potter. 1980. Genetic considerations in plasmacytomas of BALB/c, NZB and (BALB/c × NZB)_F₁ mice. In *Progress in Myeloma*. M. Potter, editor, Elsevier North-Holland Biomedical Press, Amsterdam. 263.
17. Léonard, A., and G. H. DeKnudt. 1967. 6 new markers for chromosome studies in the mouse. *Nature (Lond.)*. 214:504.

18. Wang, H. C., and S. Fedoroff. 1971. Banding of human chromosomes treated with trypsin. *Nature (Lond.)*. 235:52.
19. Committee on Standardized Genetic Nomenclature For Mice. 1972. Standard karyotype of the mouse. *Mus musculus*. *J. Hered.* 63:69.
20. Rybak, J., P. Tharadel, S. Robinett, M. Garcia, G. Mankinen, and M. Freeman. 1982. A simple reproducible method for prometaphase chromosome analysis. *Hum. Genet.* 60:328.
21. Nesbitt, M. N., and U. Francke. 1973. A system of nomenclature for band patterns of mouse chromosomes. *Chromosoma*. 41:145.
22. Klein, G. 1981. Change in gene dosage and gene expression: a common denominator in the tumorigenic action of viral oncogenes and non-random chromosomal changes? *Nature (Lond.)*. 294:313.
23. Crews, S., R. Barth, L. Hood, J. Prehn, and C. Calame. 1982. Mouse *c-myc* oncogene is located on chromosome 15 and translocated to chromosome 12 in plasmacytomas. *Science (Wash. DC)*. 218:1319.
24. Cory, S., S. Gerondakis, and J. Adams. 1983. Interchromosomal recombination of the cellular oncogene *c-myc* with immunoglobulin heavy chain locus in murine plasmacytomas is a reciprocal exchange. *EMBO (Eur. Mol. Biol. Org.) J.* 2:697.
25. Cory, S., J. Adams, S. Gerondakis, J. F. A. P. Miller, J. Gamble, F. Wiener, and J. Spira. 1983. Fusion of DNA region to murine immunoglobulin heavy chain locus corresponds to plasmacytoma associated chromosome translocation. *EMBO (Eur. Mol. Biol. Org.) J.* 2:213.
26. Stanton, L. W., R. Watt, and K. B. Marcu. 1983. Translocation, breakage and truncated transcripts of *c-myc* oncogene in murine plasmacytomas. *Nature (Lond.)*. 303:401.
27. Klein, G. 1983. Specific chromosomal translocations and the genesis of B-cell derived tumors in mice and men. Minireview. *Cell*. 32:311.