Proc. Natl. Acad. Sci. USA
Vol. 81, pp. 5826–5830, September 1984
Genetics

Human c-*fos* oncogene mapped within chromosomal region 14q21 → q31

(gene mapping/cancer genetics/Southern blots/*in situ* hybridization)

P. E. BARKER*, MARK RABIN*, MICHAEL WATSON†, W. ROY BREG†, FRANK H. RUDDLE*†, AND INDER M. VERMA‡

Departments of *Biology and of †Human Genetics, Yale University, New Haven, CT 06520; and ‡Molecular Biology and Virology Laboratory, The Salk Institute, San Diego, CA 92138

Contributed by Frank H. Ruddle, June 4, 1984

ABSTRACT **The human cellular homolog (c-*fos*) of the transforming gene of Finkel–Biskis–Jinkins (FBJ) murine osteosarcoma virus was mapped to a single human chromosome. DNA from a series of 31 mouse–human somatic cell hybrid lines was probed with v- and c-*fos* molecular clones by Southern blotting. Human c-*fos* segregated with the distal region of the long arm of human chromosome 14. *In situ* hybridization of ^{125}I-labeled human c-*fos* probe to normal human metaphase chromosomes independently confirmed these results and localized the c-*fos* oncogene to region 14q21 → q31.**

Acutely transforming retroviruses induce neoplasia *in vivo* and transform fibroblasts *in vitro* (1, 2). Their genomes contain sequences (v-*onc*) that have counterparts in host chromosomal DNA (1, 3). Acquisition of cellular sequences (c-*onc*) by replication-competent retroviruses imparts to them the ability to induce rapid neoplasia. Although several c-*onc* genes are expressed in a variety of cell lines and in normal pre- and postnatal tissues (4–10) and some c-*onc* gene products have been identified (11–13), their role in normal cellular metabolism remains largely conjectural. Evolutionary conservation of many c-*onc* sequences implies that c-*onc* genes play important roles in the biology of the organism (14, 15).

Genetic rearrangements detected in karyotypes and at certain oncogene loci have been reported for several types of human and murine malignancies (16–18). The biological consequences of these rearrangements have not been clearly defined. The human oncogene c-*fos* is homologous to the Finkel–Biskis–Jinkins (FBJ) murine osteosarcoma virus oncogene (19). Expression of c-*fos* appears to be limited during normal development to the extraembryonic tissues (20); however, c-*fos* transcripts have been detected in many human malignancies (21). Therefore, it was of interest to define the normal genetic map position of this oncogene. Here we report that the human *fos* gene is located at 14q21 → q31.

MATERIALS AND METHODS

Cell Lines. Mouse–human cell hybrids were derived from fusions between mouse A9 cells and various human cell lines. BDA series hybrids were constructed from GM589, a human fibroblast line that carries a balanced reciprocal translocation between chromosomes 5 and 14. The translocation products are t(5;14)(5qter → 5p14::14q21 → 14qter) and a smaller chromosome t(14;5)(14pter → 14q21::5p14 → 5pter). Thus, in the BDA series hybrids, the nucleoside phosphorylase (NP) locus at 14q13.1 (22) segregated with the smaller translocation chromosome t(14;5) and pAW101, a human chromosome 14 marker (D14S1; ref. 23), segregated with t(5;14). The AHA series human parent was GM144. The 41pT and FRY series were fusion products of A9 with GM126. The WAV series was constructed with WI-38 fibroblasts. Cytogenetic and isozyme analyses were performed concurrently with DNA isolation as reported (24).

DNA Probes. Probes for human c-*fos* genes included three pBR322 derivatives containing *fos*-related sequences. The p.fos-1 probe contained a 1.1-kilobase (kb) *Pst* I fragment from the oncogene of FBJ virus (25). The 3.1 probe consisted of a 3.1-kb *Nco* I–*Xho* I fragment from the cloned human c-*fos* locus (26). pHVV (27) was a cloned chimeric *fos* gene containing a 5′ *Eco*RI–*Nco* I human *fos* sequence linked to the 3′ region of the viral *fos* gene, including the 3′ long terminal repeat. The *fos* regions of all three probes showed homology at high stringency conditions (15 mM NaCl/1.5 mM sodium citrate, 65°C) and each detected a 9.0-kb band in *Eco*RI-cleaved human genomic DNA (26). The v-*fos* or c-*fos* 3.1 probe inserts were used to detect the human genomic band in blotting experiments. *In situ* hybridization experiments employed the entire pHVV plasmid.

DNA probes used as controls for human chromosomes 2 and 14 in blotting experiments were obtained, respectively, from J. Seidman (Harvard Medical School, Boston) and R. White (University of Utah, Salt Lake City). A 3.5-kb *Eco*RI fragment of the κ light chain was excised from a recombinant bacteriophage and subcloned in pBR322. The map position of κ is 2p12 (28). The marker pAW101 (D14S1) has been regionally mapped to 14q32.1–32.2 (23).

Southern Blots. Hybrid cell DNAs were screened for *fos* with the v-*fos* probe as described (25, 29, 30). For blots of hybrid DNAs with the 3.1 genomic c-*fos* probe, the 3.1-kb insert was excised from the plasmid by sequential digestion with *Nco* I and *Xho* I. The probe was electroeluted, purified on an Elutip-d column (Schleicher & Schuell), and precipitated with alcohol. DNA was resuspended and then nick-translated to a specific activity of 10^8 cpm/μg with [α-^{32}P]-dCTP (3000 Ci/mmol, Amersham; 1 Ci = 37 GBq). Cellular hybrid DNAs and controls were digested, electrophoresed, blotted, and probed as reported (31).

***In Situ* Hybridization.** Metaphase chromosome spreads were prepared from human peripheral lymphocyte cultures by using standard methodology (32, 33). ^{125}I-labeled pHVV DNA containing human c-*fos* was prepared with ^{125}I-labeled dCTP (2000 Ci/mmol) by nick-translation (32). Specific radioactivity of the ^{125}I-labeled DNA probes used for *in situ* hybridization averaged 3×10^8 dpm/μg. *In situ* hybridization and autoradiography were performed according to published procedures (32, 33).

RESULTS

Hybridization Analysis. The hybridization of the v-*fos* probe to human DNAs from various cell lines is shown in

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: kb, kilobase(s); NP, nucleoside phosphorylase; FBJ, Finkel–Biskis–Jinkins.

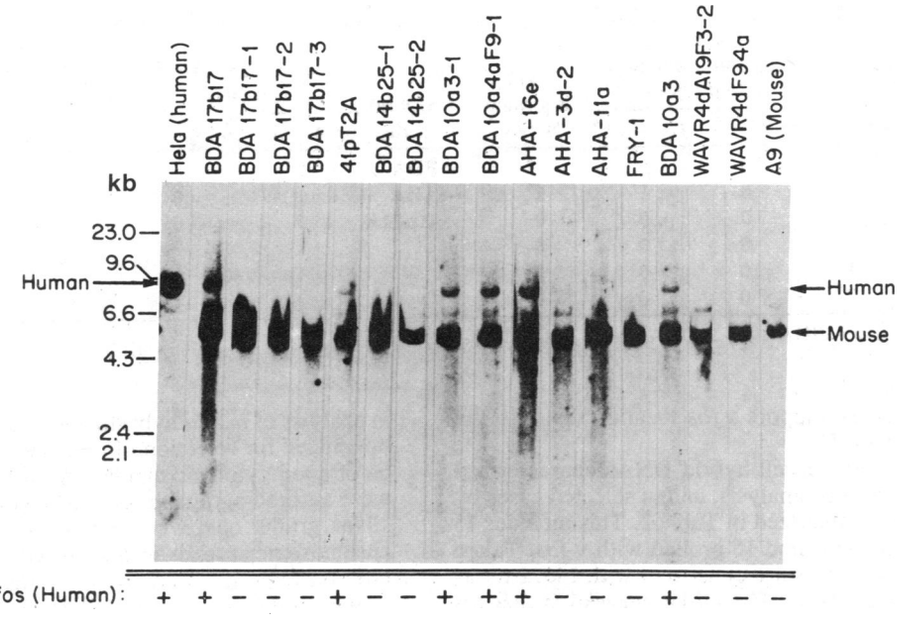

FIG. 1. Representative blotting results of 16 mouse–human somatic cell hybrid DNAs with the v-*fos* probe. The molecular weight standards (kb) are given to the left. Human control DNA is in the leftmost lane; mouse control DNA is in the rightmost lane. The human c-*fos* band (left arrow) migrates about 9.5 kb. The mouse c-*fos* band migrates at 5.5 kb. The intermediate band at 6.6 kb is nonspecific hybridization.

Fig. 1. Human DNA digested with *Eco*RI and hybridized to v-*fos* shows a single 9.0-kb band, whereas mouse DNA contains a single band of about 5.5 kb (24). The mouse-specific band is detected in all cell lines, whereas the human 9.0-kb band appears in only a few. The composite analysis of human specific *fos* hybridization is tabulated at the bottom of Fig. 1. Analysis of these 16 hybrid cell DNAs with the v-*fos* probe indicated a probable assignment to human chromosome 2 or 14. Since the *fos* gene detected with the v-*fos* probe showed 4/16 hybrids discordant for NP, it appeared most likely that *fos* was on chromosome 2. These preliminary data have been published in abstract form (34, 35).

To confirm the chromosome 2 location and rule out chromosome 14, four 41pT2A subclones were blotted with a chromosome 2 probe (28), with *fos* probes and with a chromosome 14 probe (pAW101). DNAs cut with *Bam*HI and probed with the entire v-*fos* probe showed the presence of human c-*fos* in each of the four subclones as a 6.0-kb band. The filter was stripped and rehybridized with the κ probe for chromosome 2. Chromosome 2 was present in 41pT2A-24 but absent from 41pT2A-2, -4, and -18 (not shown). A second set of the same hybrid DNAs was cut with *Eco*RI and hybridized with the 3.1-kb c-*fos* probe (Fig. 2*a*). The diagnostic 9.0-kb *Eco*RI human band (H) is present in each subclone. When the filter was stripped and rehybridized with pAW101, hybridization was detected in each of the subclones as a 17-kb band (H) (Fig. 2*b*). The human control DNA in Fig. 2*b* (lane 1) is heterozygous for the pAW101 probe. These results show concordance between pAW101 and *fos*. The results indicated that the human *fos* gene was on chromosome 14, not chromosome 2.

Additional cell hybrids were screened for c-*fos* with the 3.1-kb human genomic probe (data not shown). In 13 of 15 hybrid cell DNAs, c-*fos* segregated with the NP locus. In 2 of the 15, c-*fos* segregated independently of NP. The 4 discordant hybrid cell DNAs from the first mapping experiment with v-*fos* probe (DNA 10a3-1, -4, -6, and BDA17b17) and the 2 discordant hybrids from experiments with c-*fos* (BDA10a3 and AHA16e3) were then studied in detail. AHA16e3 contained pAW101 and human *fos* by hybridization analysis, but NP expression was not detected on multiple assays. We believe this single discordancy can be explained by NP nonexpression or chromosome rearrangement. The remaining 5 discordant cell hybrid DNAs were all from the BDA series and were segregating the GM589 balanced translocation between chromosomes 5 and 14. Since NP is proximal to the translocation breakpoint and pAW101 is distal, the pAW101 probe served as a molecular marker for t(5;14) in hybrids lacking NP expression. The presence of human *fos*, pAW101, and NP expression are compared in Table 1. Since *fos* segregated with pAW101 but not with NP,

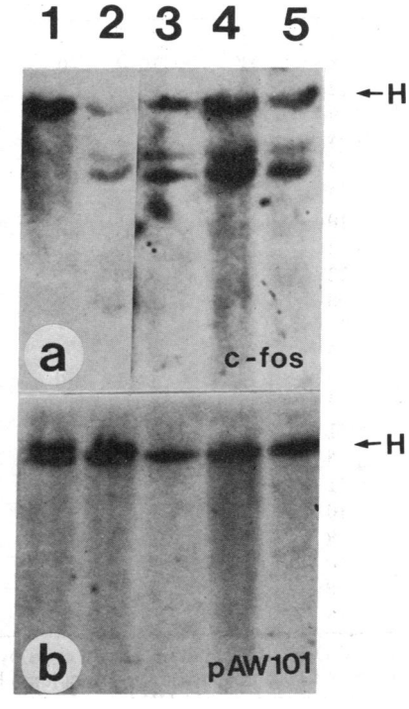

FIG. 2. *Eco*RI-cleaved DNAs from 41pT2A subclones (lanes 2–5) hybridized with c-*fos* probe (*a*) and chromosome 14 probe (*b*). Lane 1, human control DNA; lanes 2–5, 41pT2A-2, -4, -18, and -24, respectively.

Table 1. Human c-*fos* segregates with pAW101 but not with NP in BDA series somatic cell hybrids

Hybrid series	Number of concordant hybrid cell DNAs		Number of discordant hybrid cell DNAs		Total discordant DNAs
	NP^+/fos^+	NP^-/fos^-	NP^+/fos^-	NP^-/fos^+	
BDA	1	7	0	5*	5*
AHA	2	3	0	1†	1†
41pT2A	6	0	0	0	0
FRY4	3	0	0	0	0
FRY1	0	1	0	0	0
WAV	0	2	0	0	0

Hybrid series	Number of concordant hybrid cell DNAs		Number of discordant hybrid cell DNAs		Total discordant DNAs
	pAW^+/fos^+	pAW^-/fos^-	pAW^+/fos^-	pAW^-/fos^+	
BDA	5	0	0	0	0
AHA	1	0	0	0	0
41pT2A	5	0	0	0	0

*Hybrid DNAs BDA 10a3, BDA 10a3-1, BDA 10a3-4, BDA 10a3-6, BDA 17b17.
†AHA 16e3.

the BDA discordancies support a *fos* location distal to the BDA breakpoint at 14q21.

Mapping results with 31 cell hybrid DNAs characterized by isozyme and karyotype analysis, and in selected cases by DNA markers, are summarized in Table 2. This includes 15 hybrids probed with c-*fos* and 16 probed with v-*fos*. Taken together, these experiments are consistent with 14q21-ter as the location of human c-*fos*. The initial suggestion that *fos* was on human chromosome 2 was ruled out.

In situ hybridization of ^{125}I-labeled pHVV DNA to human metaphase chromosomes was performed to determine the c-*fos* gene locus independent of the mapping studies described above. Chromosome spreads were G-banded and photographed prior to hybridization. This approach precluded bias in analysis of *in situ* hybridization data since the only criterion applied for selection of metaphase spreads was that they be of good cytologic quality. After hybridization, the slides were autoradiographed for 7–21 days and the distribution of silver grains observed over 43 previously photographed chromosome spreads was analyzed. The number of nonspecific background grains was low (approximately equivalent to the number associated with chromosomes). A total of 100 grains was observed over chromosomes (data not shown), of which 47 were assigned to chromosome 14. An average accumulation of about 2 grains per chromosome was observed as background. Analysis of the distribution of silver grains associated with chromosome 14 revealed that 40 (85%) were localized within the region q21 → q31 (Fig. 3*a*). Statistical analysis of the number of grains per chromosome unit by Poisson distribution indicated a highly significant ($P < 10^{-17}$) concentration within this region. To confirm this localization, ^{125}I-labeled pHVV DNA was hybridized to metaphase spreads from a normal individual carrying a familial 14p+ marker chromosome (36). The distinct morphology of this marker chromosome permitted positive identification after *in situ* hybridization without prior G-banding (Fig. 3*b*). Analysis of 23 cells revealed that 14 (61%) contained a labeled 14p+ marker chromosome that consistently showed extensive hybridization within region q21 → q31.

Table 2. Assignment of human c-*fos* oncogene to human chromosome 14 by Southern blotting of 31 somatic cell hybrid DNAs with cloned probes for v- and c-*fos*

Human chromosome	Number of concordant hybrid cell DNAs		Number of discordant hybrid cell DNAs		Total discordant DNAs
	+/+	−/−	+/−	−/+	
1	3	5	15	4	19
2	8	11	11	0	11
3	12	5	0	5	5
4	9	7	6	4	10
5	5	5	11	4	15
6	8	10	10	2	12
7	2	9	15	0	15
8	10	8	3	2	5
9	2	10	12	1	13
10	12	10	5	1	6
11	8	9	11	3	14
12	11	11	8	1	9
13	5	7	9	4	13
14	17	13	1*	0	1*
15	7	11	12	1	13
16	11	7	6	2	8
17	5	8	14	2	16
18	11	10	7	1	8
19	10	9	9	3	12
20	9	8	10	4	14
21	10	9	8	5	13
22	8	4	2	4	6
X	18	5	0	5	5

+/+, Hybrid cell DNAs that contain human c-*fos* by DNA blotting and the numbered chromosome in the left column by isozyme, karyotype, and, in selected cases, DNA marker analysis. −/−, fos^-, chromosome$^-$. +/−, fos^+/chromosome$^-$. −/+, fos^-/chromosome$^+$. Hybrids that could not be clearly scored + or − for a human chromosome were not included in the summary.
*AHA 16e3.

DISCUSSION

The c-*fos* (Human) Gene Lies Between 14q21 and 14q31. The human c-*fos* gene has been molecularly cloned and its complete nucleotide sequence has been determined (37). Comparison of the v- and human c-*fos* genes shows that the cellular gene contains three intervening sequences and can encode a protein of 380 amino acids. Transcripts of 2.2 kb from human c-*fos* genes have been detected in cultured human cells (37), in human placenta (37), and in various human malignancies (21). Because the FBJ murine sarcoma virus v-*fos* gene and human c-*fos* share >90% nucleotide sequence homology, the v-*fos* probe could be used to detect the human gene in somatic cell hybrid DNAs. Several hybrid cell lines contained sequences homologous to v- and c-*fos* probes (Figs. 1 and 2). Comparison between the subsets of human chromosomes present in various hybrids and the presence of human c-*fos* by Southern blotting indicate that the human c-*fos* gene segregates with the chromosome 14 marker NP in most cell hybrids (Table 2). Further, concordant segregation in the BDA hybrids between c-*fos* and pAW101, but not c-*fos* and NP, suggested that the c-*fos* gene is located distal to the BDA chromosome 14 breakpoint at 14q21 (Table 1).

In situ hybridization of ^{125}I-labeled pHVV to human metaphase chromosomes independently confirmed the map location suggested by the hybrid cell panel data and localized the c-*fos* gene to the region 14q21 → q31. The pHVV probe proved more useful for *in situ* hybridization experiments than p.fos-1, because of its more extensive homology to the

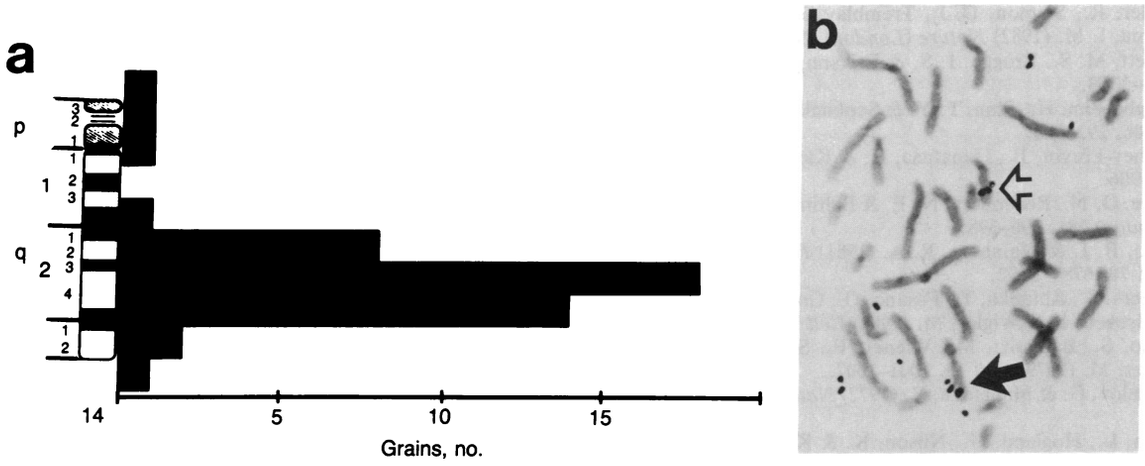

FIG. 3. Subchromosomal localization of the human c-*fos* oncogene. (*a*) Distribution of silver grains observed over chromosome 14 (n = 19 labeled chromosomes). The chromosome was divided into units scaled to the average diameter of a silver grain (0.35 μm). Of 47 total grains assigned to chromosome 14, 40 (85%) were localized to region q21 → q31. A range of ±1 grain diameter around the histogram peak is assumed. (*b*) *In situ* hybridization of ^{125}I-labeled pHVV to metaphase chromosomes of a male carrying a 14p+ marker chromosome (solid arrow). The normal chromosome 14 is indicated by an open arrow. (×2000.)

c-*fos* oncogene sequence. A statistically significant accumulation of autoradiographic grains was observed between bands 14q21 and 14q31 in experiments with G-banded metaphase chromosomes. A similar distribution of label was also observed over a 14p+ marker chromosome in metaphase spreads from a phenotypically normal male. These data regionally localize human c-*fos* to 14q21 → q31.

The specific role of *fos* gene products in normal and abnormal cell metabolism is not yet known. The biochemical functions of the human or viral gene products have not been defined. The v-*fos* and c-*fos* gene products are nuclear proteins (38). c-*fos* transcripts are found in many uncultured human tumors (21). In one-half of the *fos*-expressing malignant tissues, c-*fos* was overproduced up to 5-fold relative to adjacent normal tissue (21). The human and mouse c-*fos* oncogenes are expressed during development of normal extraembryonic tissues (placenta, amnion, chorion). Tissue-specific expression of *fos* during normal development argues for some specific normal function; however, its precise role remains obscure. Likewise, c-*fos* expression in malignant tissues implicates c-*fos* as of potential, albeit poorly understood, significance in the development of malignant diseases.

The FBJ virus complex induces in NIH Swiss mice a unique type of chondroosseus neoplasia derived from the periosteal cells, resembling human juxtacortical osteosarcoma (39). The original virus complex was isolated from a spontaneous osteosarcoma of a CF1 mouse. Among inbred strains of mice, C3H sublines and hybrids have the highest frequency of spontaneous osteosarcoma (<1%) (40). The possible involvement of *fos* has not been examined. In the mouse, the c-*fos* locus resides on murine chromosome 12 (P. D'Eustachio, personal communication). Both human chromosome 14 and mouse chromosome 12 contain the immunoglobulin heavy chain loci and may represent evolutionary conservation of the *fos–Igh* linkage group. Among humans, Gardner syndrome manifests as benign soft tissue and bone tumors and intestinal adenomas that are predisposed to malignancy (41). The Gardner syndrome segregates as a single autosomal dominant gene, but its exact chromosomal location has not been reported. The involvement of v-*fos* in murine osteosarcomas of viral etiology makes this gene and its cellular homologue c-*fos* of potential interest in relation to Gardner syndrome. For linkage studies, human c-*fos* gene exhibits some polymorphism (42). Human c-*fos* gene at 14q21 → q31 is in proximity to the highly polymorphic pAW101 locus at 14q32.1 → q32.2 and may be close enough to make the latter of practical value in family studies.

Human malignancies that have been associated with chromosome 14-specific breakage include childhood acute lymphocytic leukemia (43), malignant lymphoma (44), and some forms of Burkitt lymphoma (45). None of these disorders shows breakpoints within the region 14q21 → q31. However, cytogenetic studies of papillary serous adenocarcinomas of the ovary have revealed a nonrandom reciprocal translocation t(6;14)(q21;q24) that appears to be characteristic of this malignancy (46). The breakpoint at 14q24 observed in these tumors is centered within the region of chromosome 14 where we have mapped c-*fos*. Coincidentally, another human oncogene, c-*myb*, which is homologous to the oncogene of avian myeloblastosis virus, has been localized within the region 6q22 → q24 (47). The relationships between such translocations and the possible involvement of c-*fos* in malignant transformation, while provocative, remain unknown.

We thank A. D. Miller for pHVV and thank John Hart, Christine Gillies, Ann Hughes, Marilyn Newman, and Marie Siniscalchi for their help with this work. I.M.V. was supported by grants from the National Institutes of Health and the American Cancer Society. P.E.B. is a postdoctoral fellow of the Muscular Dystrophy Association. M.R. is a postdoctoral fellow of the Leukemia Society of America. M.W. and W.R.B. were supported by National Institute of Child Health and Human Development Grant HD 11624. This work was supported by National Institutes of Health Grant GM09966 (F.H.R.).

1. Bishop, J. M. & Varmus, H. E. (1982) in *RNA Tumor Viruses, Molecular Biology of Tumor Viruses*, eds. Weiss, R., Teich, N., Varmus, H. E. & Coffin, J. (Cold Spring Laboratory, Cold Spring Harbor, NY), 2nd Ed., pp. 999–1108.
2. Bishop, J. M. (1978) *Annu. Rev. Biochem.* **47**, 35–88.
3. Bishop, J. M. (1982) *Sci. Am.* **246**, 80–92.
4. Chen, J. H. (1980) *J. Virol.* **36**, 162–170.
5. Gonda, T. J., Sheiness, D. K. & Bishop, J. M. (1982) *Mol. Cell. Biol.* **2**, 617–624.
6. Shibuya, M., Hanafusa, H. & Balduzzi, P. C. (1982) *J. Virol.* **42**, 143–152.
7. Westin, E. H., Wong-Staal, F., Gleman, E. P., Dalla-Favera, R., Papas, T. S., Lautenberger, J. A., Eva, A., Reddy, E. P., Tronick, S. R., Aaronson, S. A. & Gallo, R. C. (1982) *Proc. Natl. Acad. Sci. USA* **79**, 2490–2492.
8. Westin, E. H., Gallo, R. C., Arya, S. K., Era, A., Souza, L. M., Baluda, M. A., Aaronson, S. A. & Wong-Stahl, F. (1982) *Proc. Natl. Acad. Sci. USA* **79**, 2194–2198.

9. Muller, R., Slamon, D. J., Tremblay, J. M., Cline, M. J. & Verma, I. M. (1982) *Nature (London)* **299,** 640–644.
10. Collett, M. S., Brugge, J. S. & Erikson, R. L. (1978) *Cell* **15,** 1363–1369.
11. Langbeheim, H., Shih, T. Y. & Scolnick, E. M. (1980) *Virology* **106,** 292–300.
12. Mathey-Prevot, B., Hanafusa, H. & Kawai, S. (1982) *Cell* **28,** 897–906.
13. Witte, O. N., Rosenberg, N. E. & Baltimore, D. (1979) *Nature (London)* **281,** 396–398.
14. Shilo, B. J. & Weinberg, R. A. (1981) *Proc. Natl. Acad. Sci. USA* **78,** 6789–6792.
15. Powers, S., Kataoka, T., Fasano, O., Goldfarb, M., Strathern, J., Broach, J. & Wigler, M. (1984) *Cell* **36,** 607–612.
16. Ohno, S., Babonitz, M., Wiener, F., Spiro, J., Klein, G. & Potter, M. (1979) *Cell* **18,** 1001–1007.
17. Manalov, G. & Manalova, Y. (1972) *Nature (London)* **237,** 33–34.
18. Zech, L., Hogland, U., Nilson, K. & Klein, G. (1976) *Int. J. Cancer* **17,** 47–56.
19. Curran, T., MacConnel, W. P., van Straaten, F. & Verma, I. M. (1983) *Mol. Cell. Biol.* **3,** 914–921.
20. Muller, R., Tremblay, G. M., Adamson, E. D. & Verma, I. M. (1983) *Nature (London)* **304,** 454–456.
21. Slamon, D. J., deKernion, J. B., Verma, I. M. & Cline, M. J. (1984) *Science* **224,** 256–262.
22. Remes, G. M., Fisher, R. A., Hackel, E., Coucineau, A. J. & Higgins, V. J. (1984) *Cytogenet. Cell Genet.* **37,** 568 (abstr.).
23. Donlon, T. A., Litt, M., Newcom, S. R. & Magenis, R. E. (1983) *Am. J. Hum. Genet.* **35,** 1097–1106.
24. Ryan, J., Barker, P. E., Shimizu, K., Wigler, M. & Ruddle, F. H. (1983) *Proc. Natl. Acad. Sci. USA* **80,** 4460–4463.
25. Curran, T., Peters, G., Van Beveren, C., Teich, N. M. & Verma, I. M. (1982) *J. Virol.* **44,** 674–682.
26. van Straaten, F., Muller, R., Curran, T., van Beveren, C. & Verma, I. M. (1983) *Proc. Natl. Acad. Sci. USA* **80,** 3183–3187.
27. Miller, A. D., Curran, T. & Verma, I. M. (1984) *Cell* **36,** 51–60.
28. Rabbitts, T. H. (1983) *Biochem. Soc. Trans.* **11,** 119–125.
29. Verma, I. M., Lei, M. H.-T., Bosselma, R. A., McKennett, M. A., Fan, H. & Berns, A. (1980) *Proc. Natl. Acad. Sci. USA* **77,** 1773–1777.
30. Southern, E. M. (1975) *J. Mol. Biol.* **98,** 503–517.
31. Roussel, M. F., Sherr, C. J., Barker, P. E. & Ruddle, F. H. (1983) *J. Virol.* **48,** 770–773.
32. Rabin, M., Watson, M., Barker, P. E., Ryan, J., Breg, W. R. & Ruddle, F. H. (1984) *Cytogenet. Cell Genet.* **38,** 70–72.
33. Rabin, M., Uhlenbeck, O. C., Steffensen, D. M. & Mangel, W. F. (1984) *J. Virol.* **49,** 445–451.
34. Barker, P. E., Ruddle, F. H. & Verma, I. M. (1983) in *RNA Tumor Viruses*, ed. Scolnick, E. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY), p. 64.
35. Rabin, M., Watson, M., Barker, P. E., Ryan, J., Breg, W. R. & Ruddle, F. H. (1983) *Am. J. Hum. Genet.* **35,** 148 (abstr.).
36. Miller, D. A., Breg, W. R., Warburton, D., Dev, V. G. & Miller, O. J. (1978) *Hum. Genet.* **43,** 289–297.
37. van Straaten, F., Muller, R., Curran, T., van Beveren, C. & Verma, I. M. (1983) *Proc. Natl. Acad. Sci. USA* **80,** 3183–3187.
38. Curran, T., Miller, A. D., Zokas, L. & Verma, I. M. (1984) *Cell* **36,** 259–268.
39. Ward, J. M. & Young, D. M. (1976) *Cancer Res.* **36,** 3985–3992.
40. Murphy, E. D. (1968) in *Biology of the Laboratory Mouse*, ed. Green, E. L. (Dover, New York), pp. 521–562.
41. Rasheed, S., Rhim, J. S. & Gardner, E. J. (1983) *Am. J. Hum. Genet.* **35,** 919–931.
42. Barker, D. & White, R. (1984) *Cytogenet. Cell Genet.* **37,** 224 (abstr.).
43. Williams, D. L., Look, A. T., Melvin, S. L., Roberson, P. K., Dahl, G., Flake, T. & Stass, S. (1984) *Cell* **36,** 101–109.
44. Bloomfield, C. D., Arthur, D. C., Frizzera, G., Levine, E. G., Peterson, B. A. & Gajl-Peczalska, K. J. (1983) *Cancer Res.* **43,** 2975–2984.
45. Erickson, J., Finan, J., Nowell, P. C. & Croce, C. M. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 5611–5615.
46. Wake, N., Hreshchyshyn, M. M., Piver, S. M., Matsui, S. & Sandberg, A. A. (1980) *Cancer Res.* **40,** 4512–4518.
47. Harper, M. E., Franchini, J. L., Simon, M. I., Gallo, R. C. & Wong-Staal, F. (1983) *Nature (London)* **304,** 169–171.