**Haematology and Blood Transfusion** Vol. 29
Modern Trends in Human Leukemia VI
Edited by Neth, Gallo, Greaves, Janka


# Chromosome Alterations in Oncogenesis

P. C. Nowell[1], B. S. Emanuel[2], J. B. Finan[1], J. Erikson[3], and C. M. Croce[3]

## A. Introduction

Recently there has been increased interest in the study of chromosomal alterations in neoplastic cells. Such investigations have already begun to contribute significantly to our understanding of fundamental tumor biology, particularly with respect to the role of specific genes in carcinogenesis. This brief review will focus on this aspect of tumor cytogenetics, and particularly our own recent studies, but some generalizations will be offered first to help provide an appropriate perspective.

Based on the work from many laboratories, four general statements can be made about karyotypic alteration in neoplasia:

1. Most tumors have chromosome abnormalities. These usually are not present in other cells of the body.
2. In a given tumor, all the neoplastic cells often have the same cytogenetic change, or related changes.
3. Chromosome abnormalities are more extensive in advanced tumors.
4. Chromosome alterations are frequently different between tumors, but there are nonrandom patterns.

1 Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA
2 The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
3 The Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania, USA

The cytogenetic findings that support the first two statements represent a significant portion of the increasing evidence that somatic genetic changes are important in tumorigenesis. In addition, the second generalization, along with related biochemical and immunoglobulin data, has been the basis for the now generally accepted view that most neoplasms are unicellular in origin [1, 2]. The fact that in a given tumor all of the cells show the same chromosome abnormality (or related abnormalities) suggests the origin of the tumor from a single altered cell. Presumably, the particular karyotypic change confers on the progenitor cell a selective growth advantage, allowing its progeny to expand as a neoplastic clone [1].

The third generalization listed has also contributed to our understanding of the natural history of tumor development. The observation that more advanced neoplasms typically show more extensive karyotypic alterations has led to the suggestion that clinical and biologic tumor progression may reflect the appearance in a neoplastic clone, over time, of subpopulations of cells with increasingly altered genetic makeup [1, 3]. Experimental evidence indicates that neoplastic cells show increased genetic instability, and so are more likely than normal cells to generate genetic variants [3]. Occasionally, such a variant cell may have more aggressive biologic characteristics, and so its progeny may grow out as the predominant malignant population, providing the basis for clinical tumor progression.

This concept has been well documented in chronic granulocytic leukemia, where

the cells in the early indolent stage of the disorder typically show only the Philadelphia chromosome, but the terminal accelerated phase of the disease apparently results from overgrowth of this initial population by one or more subclones having additional karyotypic changes [4]. A similar sequence of events has been documented in other human and experimental tumors [3]. It has also been possible, through cytogenetic studies, to demonstrate the coexistence of multiple variant subpopulations within many advanced malignancies, thus providing at least one explanation for the biologically and clinically important phenomenon of tumor cell heterogeneity [3, 4].

## B. Nonrandom Chromosome Abnormalities in Neoplasia

It is the final generalization listed that has engendered most of the very recent interest in tumor cytogenetics. With improved staining methods, it has become increasingly apparent that specific alterations in particular chromosomes are associated, with varying degrees of consistency, with specific types of tumors or with neoplasia in general [4, 5]. It has been hypothesized that these nonrandom karyotypic changes are indicating sites in the genome where particular genes, important in carcinogenesis, may be located, and also how the function of these "oncogenes" might be significantly altered [4–6]. In some instances, the consistent abnormality has been the gain or loss of a whole chromosome, or parts of a chromosome, suggesting a critical role for gene dosage in oncogenesis [4–6]. This has also been suggested by the observation in tumor cells of unusual chromosome structures that include elongated homogeneously staining regions (HSR), small extrachromosomal paired chromatin bodies – double minutes (DM), and abnormal banded regions (ABR), that all apparently represent alternative forms of gene amplification [7, 8].

Specific reciprocal chromosome translocations, without apparent addition or loss of genetic material, have also been identified as occurring nonrandomly in a variety of neoplasms, particularly leukemias and lymphomas [1, 4, 5]. Because such translocations, as well as a few of the HSR-type aberrations, are the only karyotypic abnormalities in tumor cells which thus far have been clearly related to altered function of known oncogenes, the remainder of this discussion will be restricted to these phenomena. Also, since most of the relevant data have been derived from hematopoietic neoplasms, only limited reference will be made to findings in other types of tumor.

## C. Chromosome Translocations and Oncogenesis

Cytogenetic details of a number of the translocations recognized in various human leukemias and lymphomas have been the subject of several recent reviews [4, 5]. It has been suggested that their importance in carcinogenesis results from position effects, with the translocation bringing an inactive "proto-"oncogene into juxtaposition with "activating" sequences elsewhere in the genome [4, 6]. This hypothesis has now been investigated in cells of Burkitt's lymphoma, with very recent extension of such concepts to other leukemias and lymphomas. Current findings will be summarized in the subsequent sections.

### I. Burkitt's Lymphoma

In most cases of Burkitt's tumor [9, 10], there is a reciprocal translocation between chromosomes 8 and 14. Variant translocations have been described in a small minority of these neoplasms [11, 12], one involving chromosomes 8 and 22, the other involving chromosomes 2 and 8. In all instances, the breakpoint in chromosome 8 is the same, at band q24 in the terminal portion of the long arm of the chromosome.

It has also been shown [13–16] that the genes for human immunoglobulin heavy chains map to chromosome 14, for $\lambda$ light chain genes to chromosome 22, and for the $\kappa$ light chain genes to chromosome 2. At the same time, one of the human homologs of known retroviral oncogenes, the so-called c-*myc* gene that is homologous to the

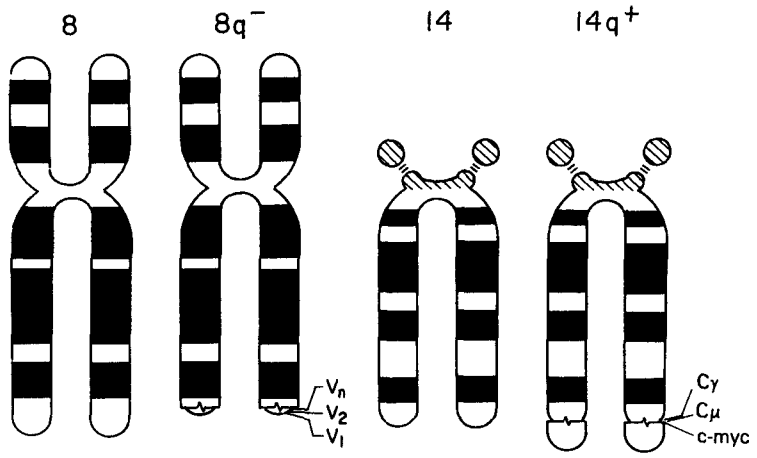


**Fig. 1.** Diagram of the t(8; 14) chromosome translocation in a Burkitt's lymphoma cell line. The $V_H$ genes translocate from chromosome 14 to the involved chromosome 8 (8q–), while the c-*myc* oncogene translocates to the heavy chain locus, and shows greatly increased transcriptional activity in its new location. Reproduced from [21]

avian virus oncogene v-*myc*, was found [17, 18] to be located on the terminal portion of the long arm of chromosome 8. These observations suggested that the immunoglobulin genes and the c-*myc* oncogene might have important roles in the development of Burkitt's tumor, and this has subsequently been demonstrated, in our laboratory and by others, to be the case.

It was first shown, in a Burkitt's tumor cell line [19], that the immunoglobulin heavy chain locus in these cells was split, with a portion translocated to the involved chromosome 8, and a portion retained on chromosome 14. Subsequently, similar methods were used to show that the segment of chromosome 8 translocated to the long arm of chromosome 14 contained the c-*myc* oncogene [17, 18, 20], as shown in Fig. 1. It was also demonstrated [21] that in its new location, adjacent to a transcriptionally active immunoglobulin gene, the c-*myc* oncogene showed markedly increased transcription.

These studies have since been extended to Burkitt's lymphomas with the variant 8;22 and 2;8 chromosome translocations, using both somatic cell genetic and in situ hybridization methods [22–25]. In these circumstances, the results again indicate involvement of both the c-*myc* gene and an immunoglobulin gene, but with interesting differences in the apparent mechanism of activation of the oncogene. In a study of a Burkitt's lymphoma cell line with the 8;22 translocation, we found [23] that the c-*myc* gene remains on the number 8 chromosome, and the constant region portion of the $\lambda$ light chain gene is translocated from chromosome 22 to this chromosome 8. The c-*myc* oncogene on the rearranged chromosome 8 (8q+) shows enhanced transcriptional activity as a result of the translocation, whereas the c-*myc* oncogene on the normal chromosome 8 is transcriptionally silent [23]. Similar results have been obtained with a Burkitt's cell line containing the variant 2;8 chromosome translocation that involves the $\kappa$ light chain locus [24, 25], and here again it was possible to demonstrate that high levels of transcripts of the c-*myc* gene were found when it resided on the 8q+ chromosome, but not on the normal chromosome 8.

Taken together, these various findings with Burkitt's lymphomas clearly suggest that a chromosomal rearrangement in a B lymphocyte that places the c-*myc* oncogene adjacent to a transcriptionally active immunoglobulin gene can lead to markedly increased transcription of the oncogene in circumstances where it is not normally active. Additional support for this conclusion comes from concurrent observations with mouse plasmacytomas, in which it recently has been shown that a characteristic nonrandom chromosomal translocation involves the same immunoglobulin and *myc* genes as in Burkitt's tumor [26], with the same effect of increased transcription of c-*myc* [27]. The same circumstance may also obtain in the rat [28]. It is not yet clear to what extent such findings may be applicable to other hemic tumors, but the results have stimulated initial investigations in a number of directions. Several of these will be summarized briefly in the next section.

## II. Other Human Leukemias and Lymphomas

A number of lymphomas have translocations that involve the terminal portion of 14q (band q32) and either the long arm of chromosome 11 (q13) or the long arm of chromosome 18 (q21) [29, 30]. It appeared very likely that these rearrangements might involve the immunoglobulin heavy chain locus, as in the 8; 14 translocation of Burkitt's tumor. At present, however, there is no candidate oncogene that has been mapped to the relevant regions of 11q and 18q that might be activated in the same fashion as the c-*myc* gene in Burkitt's tumor.

We have recently begun to study a number of these translocations, and have cloned the chromosomal breakpoint of a human B cell tumor with the characteristic 11; 14 translocation already mentioned [31]. We have found [32] that the breakpoint is indeed within the immunoglobulin heavy chain locus on chromosome 14. Furthermore, it was possible to demonstrate that DNA sequences from chromosome 11 had been translocated immediately adjacent to the breakpoint on the involved chromosome 14 and that these chromosome 11 sequences were rearranged. This rearranged DNA segment was also present in the cells of another B cell lymphoma with the same 11; 14 translocation, but not in Burkitt's lymphoma cells with the 8; 14 translocation or in non-neoplastic human lymphoblastoid cells [31]. Thus, it may be possible to identify and characterize a gene, for which we have suggested the name bcl-1, located at band q13 of chromosome 11, which appears to be involved in the malignant transformation of human B cells carrying the 11; 14 translocation. Similar studies are now under way with neoplastic B cells having the 14; 18 translocation that also occurs nonrandomly in a significant number of non-Hodgkin's lymphomas.

A different situation is found in several types of human myeloid leukemia. In these disorders, characteristic chromosomal translocations have been identified that appear to involve the human homolog of a known retroviral oncogene, but a mechanism for activation, analogous to the role of the immunoglobulin genes in the B cell tumors, has not been readily apparent.

For example, in chronic myelogenous leukemia (CML), several laboratories [33, 34] have now demonstrated that the typical t(9 ;22)(q34; q11) translocation, which produces the Philadelphia chromosome, uniformly involves translocation of the c-*abl* oncogene from its normal site on chromosome 9 to a position adjacent to the breakpoint on chromosome 22. In this new location, the c-*abl* oncogene is close to the immunoglobulin $\lambda$ light chain locus, which remains on chromosome 22 (unlike the circumstance in the 8; 22 translocation of the variant Burkitt's tumors) [35]. There is, however, evidence that in most CML cells the $\lambda$ light chain gene is not rearranged or transcriptionally active, and so it does not appear to be a likely candidate for "activating" the newly juxtaposed c-*abl* [36]. Nor is there yet strong evidence that there is an alteration in the structure or function of the translocated c-*abl* oncogene, except for one report of an abnormal RNA transcript [37]. At present, the role of c-*abl* in the pathogenesis of CML remains under active investigation.

Similar circumstances may obtain with respect to the 15; 17 chromosome translocation commonly seen in acute promyelocytic leukemia (APL) and the 8; 21 translocation that characterizes a subgroup of patients with acute myelogenous leukemia (AML) [4]. Several laboratories have been investigating the possibility that a human homolog of the retroviral oncogene erbA might be involved in the typical translocation of APL [38, 39]. We have recently obtained evidence [39] that supports the localization of this gene to the q21-22 region of human chromosome 17, closely proximal to the breakpoint in the t(15; 17)(q22; q21-22) translocation in APL [4]. Perhaps unidentified "activating" sequences are translocated from chromosome 15 and are influencing the erbA oncogene on chromosome 17, but there are as yet no specific data to support this hypothesis.

A similar phenomenon might also be occurring in those cases of AML with a characteristic t(8; 21)(q22; q22) translocation [4]. In this instance, the candidate proto-oncogene for activation is c-*mos,*

which has been mapped to the q22 region of chromosome 8, with the suggestion that sequences from 21q might be serving in the activating role [4, 5, 18]. Again, no direct data are currently available to support this concept, but our study of the c-*erbA* oncogene may have provided some relevant information. In that investigation [39], we were also able to study leukemic cells with an unusual t(17;21)(q21-22;q22) translocation involving the breakpoints on chromosomes 17 and 21 typically observed in the 15;17 translocation of APL and the 8;21 translocation of AML [40]. Here again, the erbA oncogene appeared to be located closely proximal to the breakpoint on chromosome 17, suggesting the possibility that activating sequences, in this case from chromosome 21, were being brought adjacent to it. These would be the same activating sequences presumably brought adjacent to c-*mos* in the 8;21 translocation of AML.

At present, these studies of translocations in hematopoietic tumors other than Burkitt's lymphoma are still in their early stages. It does already appear, however, that they will provide important information on other oncogenes and other activating mechanisms that could have wide applicability in tumor biology.

### D. Chromosome Alterations and Oncogene Amplification Units

As already indicated, the types of visible chromosomal changes in malignant tumors, other than translocations, that have been most definitely associated with known oncogenes to date are certain of the HSR, DM, and ABR that appear to represent gene amplification units. In earlier studies of tissue culture cell lines, it was demonstrated that these unusual cytogenetic structures represented, in some cases, multiple copies of genes necessary for cell growth under specific culture conditions [8, 41]; and also that they might be alternative forms of gene amplification, with HSR breaking down to form DM, and DM integrating into various chromosomal sites to generate HSR and ABR [7, 8]. Although these structures do not show the same consistent localization within the genome as do the nonrandom chromosome translocations, it has been shown that they can involve human homologs of retroviral oncogenes.

Perhaps most interesting is the recent report [42] that the HSR observed in a significant proportion of cases of freshly isolated neuroblastoma cells involved DNA sequences related, but not identical, to the c-*myc* oncogene. This new gene, which they designated N-*myc,* maps to the short arm of chromosome 2 in normal cells, but in the neuroblastoma cells studied, the amplified N-*myc* was found to be located at a variety of sites within the genome [42].

Related observations have been made in our laboratory and elsewhere on several cell lines derived from human carcinomas and leukemias [43–45]. For example, it has recently been demonstrated that in cells of the HL-60 cell line, originally established from a patient with APL, there are 20–40 copies of the c-*myc* gene [46, 47], and that these are associated with an ABR on chromosome 8 in the normal location of c-*myc* [45] (Fig. 2). Alitalo et al. [43] have shown similar amplification of c-*myc* in a human intestinal carcinoma cell line, related either to an HSR at an abnormal location in the genome or to DM chromosomes. In a study involving another oncogene, we have been able to demonstrate that multiple copies of the c-*abl* oncogene in the K562 cell line (from a case of CML), as well as similarly amplified copies of the C-$\lambda$ immunoglobulin gene, are associated in an ABR located on what appears to be a modified Philadelphia chromosome [44].

These various data, although still limited, certainly suggest that gene amplification units, recognizable cytogenetically as HSR, DM, and ABR, can represent another mechanism by which oncogene function may be so altered as to play a singificant role in tumorigenesis. This appears already well documented with respect to chromosomal translocations. As additional studies of oncogene structure and function are linked in the near future to various other types of nonrandom chromosomal alterations in neoplasia, it may be expected that similar associations will be made with respect to specific additions and losses of

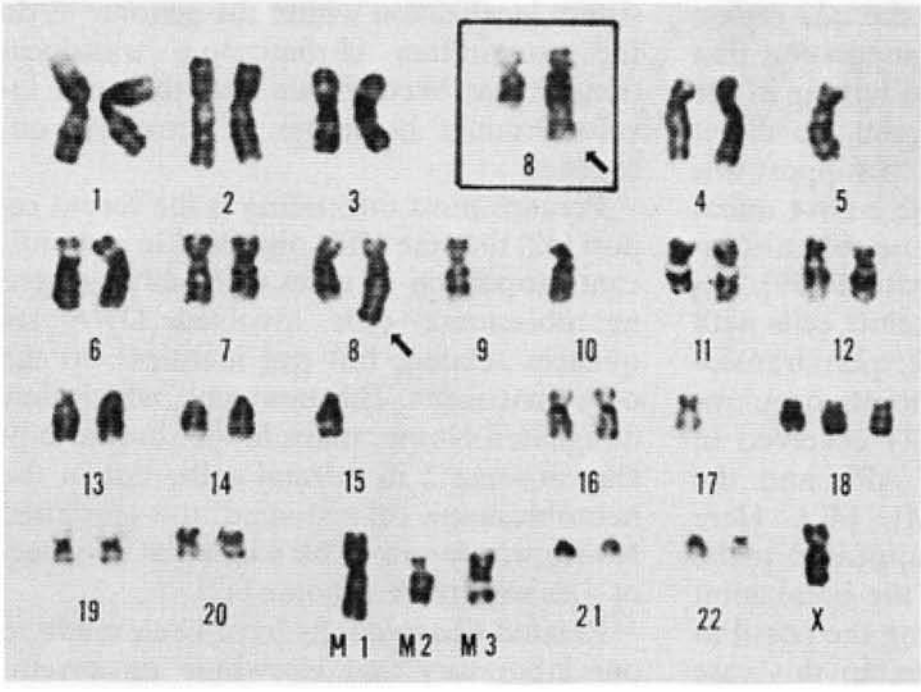


**Fig. 2.** Karyotype of human leukemic cell line HL-60, in which amplification of the c-*myc* oncogene was shown to be associated with the abnormally banded region of chromosome 8 (*arrows*). Reproduced from [45]

chromosomal material as well. It is equally clear that not all specific genetic changes important in carcinogenesis will be demonstrable through karyotypic studies, and that many will be submicroscopic, but meanwhile a wealth of visible changes are available for exploitation by combining modern cytogenetic and molecular genetic techniques.

## References


1. Nowell P (1976) The clonal evolution of tumor cell populations. Science 194:23
2. Fialkow P (1979) Clonal origin of human tumors. Annu Rev Med 30:135
3. Nowell P (1983) Tumor progression and clonal evolution: the role of genetic instability. In: German J (ed) Chromosome mutation and neoplasia. Liss, New York, p 413
4. Rowley JD, Testa JR (1983) Chromosome abnormalities in malignant hematologic diseases. In: Advances in cancer research. Academic, New York, p 103
5. Yunis JJ (1983) The chromosomal basis of human neoplasia. Science 221:227
6. Klein G (1981) The role of gene dosage and genetic transpositions in carcinogenesis. Nature 294:313
7. Balaban-Malenbaum G, Gilbert F (1977) Double minute chromosomes and the homogeneously staining regions in chromosomes of a human neuroblastoma cells line. Science 198:739
8. Biedler JL, Melera PW, Spengler BA (1983) Chromosome abnormalities and gene amplification: comparison of antifolate-resistant and human neuroblastoma cell systems. In: Rowley JD, Ultmann JE (eds) Chromosomes and cancer: from molecules to man. Academic Press, New York, p 117
9. Manolov G, Manolova Y (1972) Marker band in one chromosome 14 from Burkitt lymphoma. Nature 237:33
10. Zech L, Haglund V, Nilsson N, Klein G (1976) Characteristic chromosomal abnormalities in biopsied and lymphoid cell lines from patients with Burkitt and non-Burkitt lymphoma. Int J Cancer 17:47
11. Van den Berghe H, Paloir C, Gosseye S, Englebienne V, Cornu G, Sokal G (1979) Variant translocation in Burkitt lymphoma. Cancer Genet Cytogenet 1:9
12. Lenoir GM, Preud'homme JL, Bernheim A, Berger R (1982) Correlation between immunoglobulin light chain expression and variant translocation in Burkitt's lymphoma. Nature 298:474
13. Croce CM, Shander M, Martinis J, Cicurel L, D'Ancona GG, Dolby TW, Koprowski H (1979) Chromosomal location of the human immunoglobulin heavy chain genes. Proc Natl Acad Sci USA 76:3416
14. Erikson J, Martinis J, Croce CM (1981) Assignment of the human genes for immunoglobulin chains to chromosome 22. Nature 294:173
15. McBride OW, Heiter PA, Hollis GF, Swan D, Otey MC, Leder P (1982) Chromosomal location of human kappa and lambda im-

munoglobulin light chain constant region genes. J Exp Med 155:1480
16. Malcolm S, Barton P, Murphy C, Ferguson-Smith MA, Bentley DL, Rabbitts TH (1982) Localization of the human immunoglobulin light chain variable region genes to the short arm of chromosome 2 by in situ hybridization. Proc Natl Acad Sci USA 79:4957
17. Dalla Favera R, Bregni M, Erikson J, Patterson D, Gallo RC, Croce CM (1982) Assignment of the human c-myc onc-gene to the region of chromosome 8 which is translocated in Burkitt lymphoma cells. Proc Natl Acad Sci USA 79:7824
18. Neel B, Jhanwar S, Chaganti R, Hayward W (1982) Two human c-onc genes are located on the long arm of chromosome 8. Natl Acad Sci USA 79:7842
19. Erikson J, Finan J, Nowell PC, Croce CM (1982) Translocation of immunoglobulin $V_H$ genes in Burkitt lymphoma. Proc Natl Acad Sci USA 79:5611
20. Taub R, Kirsch I, Morton C, Lenoir G, Swan D, Tronick S, Aaronson S, Leder P (1982) Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells. Proc Natl Acad Sci USA 79:7837
21. Erikson J, ar-Rushdi A, Drwinga H, Nowell P, Croce C (1983) Transcriptional activation of the translocated c-myc oncogene in Burkitt lymphoma. Proc Natl Acad Sci USA 80:820
22. De la Chapelle A, Lenoir G, Boue J, Boue A, Gallano P, Huerre C, Szajnert M-F, Jeanpierre M, Lalouel JM, Kaplan JC (1983) Lambda Ig constant region genes are translocated to chromosome 8 in Burkitt's lymphoma with t(8;22). Nucleic Acids Res 11:1133
23. Croce C, Thierfelder W, Erikson J, Nishikura K, Finan J, Lenoir G, Rabbitts T, Nowell P (1983) Transcriptional activation of an unrearranged and untranslocated c-myc oncogene by translocation of a C-lambda locus in Burkitt lymphoma cells. Proc Natl Acad Sci USA 80:6922
24. Erikson J, Nishikura K, ar-Rushdi A, Finan J, Emanuel B, Lenoir G, Nowell PC, Croce CM (1983) Translocation of an immunoglobulin kappa locus to a region 3′ of an unrearranged c-myc oncogene enhances c-myc transcription. Proc Natl Acad Sci USA 80:7581
25. Emanuel B, Selden J, Chaganti RSK, Jhanwar S, Nowell PC, Croce CM (1984) The 2p breakpoint of a 2;8 translocation in Burkitt's lymphoma interrupts the $V_k$ locus. Proc Natl Acad Sci USA 81:2444
26. Shen-Ong GLC, Keath EJ, Piccoli SP, Cole MD (1982) Novel myc oncogene RNA from abortive immunoglobulin-gene recombination in mouse plasmacytomas. Cell 31:443
27. Marcu K, Harris L, Stanton L, Erikson J, Watt R, Croce CM (1983) Transcriptionally active c-*myc* oncogene is contained within NIARD, a DNA sequence associated with chromosomal translocations in B-cell neoplasia. Proc Natl Acad Sci USA 80:523
28. Sumegi J, Spira J, Bazin H, Szpirer J, Levan G, Klein G (1983) Rat c-myc oncogene is located on chromosome 7 and rearranges in immunocytomas with t(6;7) chromosomal translocation. Nature 306:497
29. Fukuhara S, Rowley JD, Variakojis D, Golomb HM (1979) Chromosome abnormalities in poorly differentiated lymphocytic lymphoma. Cancer Res 39:3119
30. Yunis JJ, Oken MM, Kaplan ME, Ensrud KM, Howe RR, Theologides A (1982) Distinctive chromosomal abnormalities in histologic subtypes of non-Hodgkin's lymphoma. N Engl J Med 307:1231
31. Tsujimoto Y, Yunis J, Onorato-Showe L, Nowell P, Croce C (1984) Science 224:1403
32. Erikson J, Finan J, Tsujimoto Y, Nowell P, Croce C (1984) The chromosome 14 breakpoint in neoplastic B cells with the t(11;14) translocation involves the immunoglobulin heavy chain locus. Proc Natl Acad Sci USA 81:2444
33. De Klein A, van Kessel AG, Grosveld G, Bartram CR, Hagemeijer A, Boatsma D, Spurr NK, Heisterkamp N, Groffen J, Stephenson JR (1982) A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukemia. Nature 300:765
34. Heisterkamp N, Stephenson JR, Groffen J, Hansen PF, de Klein A, Bartram CR, Grosveld G (1983) Localization of the c-abl oncogene adjacent to a translocation break point in chronic myelocytic leukaemia. Nature 306:239
35. Emanuel B, Wang E, Nowell P, Selden J, Croce C (1984) Non-identical 22q11 breakpoint for the t(9;22) of CML and the 6(8;22) of Burkitt's lymphoma. Cytogenet Cell Genet 38:127
36. Bakhshi A, Minowada J, Arnold A, Cossman J, Jensen JP, Whang-Peng J, Waldman TA, Korsmeyer SJ (1983) Lymphoid blast crises of chronic myelogenous leukemia represent stages in the development of B-cell precursors. N Engl J Med 309:826
37. Canaani E, Steiner-Saltz D, Aghai A, Gale RP, Berrebi A, Januszewicz E (1984) Altered transcription of an oncogene in chronic myeloid leukemia. Lancet 1:593

38. Spurr NK, Solomon E, Jannson M, Sheer D, Goodfellow PN, Bodmer WF, Vennstrom B (1984) Mapping of cellular oncogenes: ErbAl is on chromosome 17. EMBO J 3:159
39. Dayton AI, Selden JR, Laws G, Dorney DJ, Finan J, Tripputi P, Emanuel BS, Rovera G, Nowell PC, Croce CM (1984) A human c-*erbA* oncogene homologue is closely proximal to the chromosome 17 breakpoint in acute promyelocytic leukemia. Proc Natl Acad Sci USA 81:4495
40. Nowell P, Wilmoth D, Hoxie J, Lyss A (1984) Ph-positive acute leukemia with a 17q;21q translocation. Cancer Genet Cytogenet 12:51
41. Kaufman RJ, Brown PC, Schimke RT (1979) Amplified dihydrofolate reductase genes in unstably methotrexate-resistant cells are associated with double minute chromosomes. Proc Natl Acad Sci USA 76:5669
42. Schwab M, Alitalo K, Klempnauer K-H, Varmus HE, Bishop JM, Gilbert F, Brodeur G, Goldstein M, Trent J (1983) Amplified DNA with limited homology to myc cellular oncogene is shared by human neuroblastoma cell lines and a neuroblastoma tumor. Nature 305:245
43. Alitalo K, Schwab M, Lin CC, Varmus HE, Bishop JM (1983) Homogeneously staining chromosomal regions contain amplified copies of an abundantly expressed cellular oncogene (c-myc) in malignant neuroendocrine cells from a human colon carcinoma. Proc Natl Acad Sci USA 80:1707
44. Selden J, Emanuel B, Wang E, Cannizzaro L, Palumbo A, Erikson J, Nowell P, Rovera G, Croce C (1983) Amplified C-lambda and c-*abl* genes on the same marker chromosome in K562 leukemic cells. Proc Natl Acad Sci USA 80:7289
45. Nowell P, Finan J, Dalla Favera R, Gallo R, ar-Rushdi A, Ramanczuk P, Selden J, Emanuel B, Rovera G, Croce C (1983) Association of amplified oncogene c-*myc* with an abnormally banded chromosomes 8 in a human leukemia cell line. Nature 306:494
46. Collins S, Groudine M (1982) Amplification of endogenous *myc*-related DNA sequences in a human myeloid leukaemia cell line. Nature 298:679
47. Dalla Favera R, Wong-Staal F, Gallo RC (1982) Onc-gene amplification in promyelocytic leukaemia cell line HL-60 and primary leukaemic cells of the same patient. Nature 299:61