37. Pegram, M. D., Konecny, G. & Slamon, D. J. The molecular and cellular biology of HER2/neu gene amplification/overexpression and the clinical development of herceptin (trastuzumab) therapy for breast cancer. *Cancer Treat. Res.* **103**, 57–75 (2000).
38. Moore, M. A. The clinical use of colony stimulating factors. *Annu. Rev. Immunol.* **9**, 159–191 (1991).
39. Cho, Y., Gorina, S., Jeffrey, P. D. & Pavletich, N. P. Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations. *Science* **265**, 346–355 (1994).
40. Bhattacharjee, A. et al. Classification of human lung carcinomas by mRNA expression analysis. *Proc. Natl Acad. Sci.* (in the press).

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Online links

DATABASES
The following terms in this article are linked online to:
CancerNet: http://cancernet.nci.nih.gov/
breast cancer | colorectal cancer | prostate oncology
LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink/p53
Medscape DrugInfo:
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Glivec | Herceptin

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The Nobel Prize in Physiology or Medicine 1990:
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TIMELINE

Chromosome translocations: dangerous liaisons revisited

Janet D. Rowley

Although it has been clear for more than a century that the chromosomes in human tumour cells are often wildly abnormal, there has been controversy as to whether these changes are primary events or are merely secondary epiphenomena that reflect the genomic instability of these cells. The prevailing view for most of this period was that chromosome changes were secondary events. What happened to change this view?

Early observations that specific recurring chromosome aberrations, such as translocations, were often associated with a particular type of leukaemia, lymphoma or sarcoma led researchers to believe that chromosome rearrangements might be involved in cellular transformation. Simultaneously, technical advances, such as recombinant DNA technology and the creation of DNA probes, allowed the identification of the genes that are affected by these chromosome rearrangements. The discovery that some of these genes were the human counterparts of viral oncogenes led to the realization that rearrangements were involved in transformation. In a sense, the findings of cytogeneticists and tumour virologists validated each other — the association between oncogenes and chromosome translocations supported a role for each in human cancer pathogenesis. The recent reports that STI-571 (Glivec), a drug that inhibits the BCR–ABL fusion protein as well as other kinases, is highly effective in treating chronic myelogenous leukaemia (CML) has captured the worldwide attention of physicians, scientists and the public. The fact that this success is the result of research that started more than 40 years ago is not widely appreciated.

Early work on cancer cytogenetics

In 1890, the German biologist David von Hansemann noticed that tumour cells with chromosome abnormalities also contained several spindle bodies and other mitotic aberrations (see TIMELINE). However, Theodor Boveri provided the most comprehensive synthesis of the data and proposed that these abnormalities were the cause of malignant transformation[1]. Little was made of this observation until the 1950s, when several scientists — including Sajiro Makino in Japan, Theodore Hauschka in the United States and Albert Levan in Sweden — discovered that virtually all tumour cell lines had chromosomal aberrations, frequently containing over 100 chromosomes per cell, including DICENTRIC and RING CHROMOSOMES[2]. Cell lines from the same tumour type did not, however, have the same aberrations, so these abnormal karyotypes were assumed to be a result of the inherent genomic instability of cancer cells, rather than a cause. The view that chromosome abnormalities were an effect and not a cause of cancer persisted until the early 1970s, when the application of chromosome banding (BOX 1) allowed individual chromosomes and regions of chromosomes to be identified. This technique allowed cancer researchers to identify specific chromosome abnormalities that were often uniquely associated with human leukaemias, lymphomas and solid tumours.

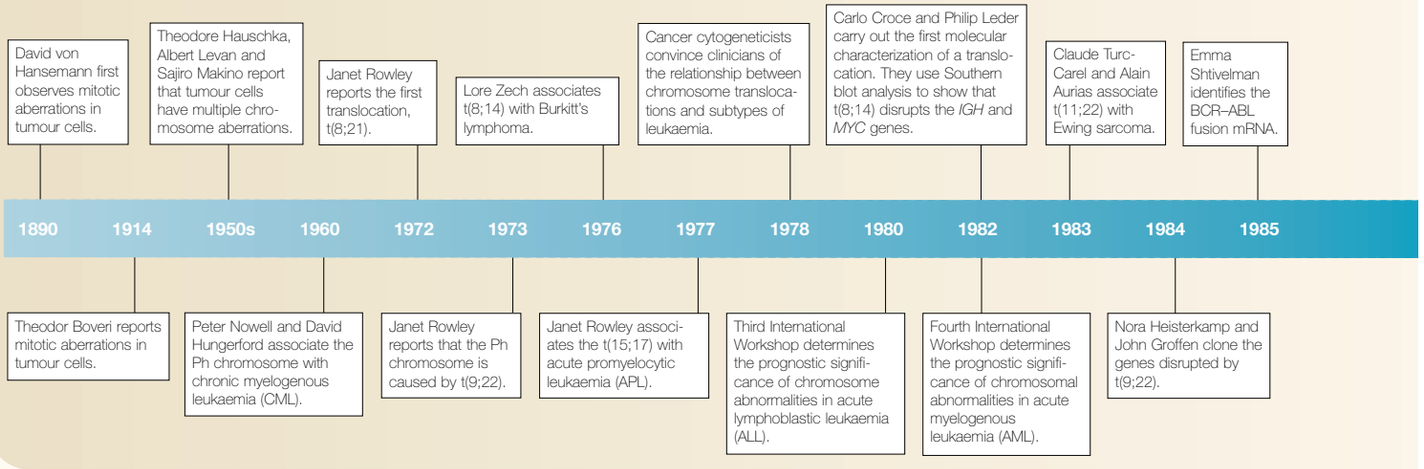
The Philadelphia story

In 1959, Peter Nowell and David Hungerford identified the first chromosome abnormality that was consistently associated with a human malignant disease. The next year, they reported that cells from CML patients had a normal number of chromosomes, but that one chromosome was too small[3]. The consistent presence of this marker chromosome in CML patients was quickly confirmed by other cancer researchers, and this marker became known as the Philadelphia or Ph[1] chromosome, now called just Ph.

This small chromosome was thought to be caused by a simple deletion, and the loss of DNA from the chromosome was proposed to be the cause of the leukaemia — an idea that was accepted for more than 10 years. The use of chromosome banding markedly changed this perception. In 1972, Rowley discovered that the Ph chromosome was not caused by a deletion, but by an interchange between the end of the long arm of chromosome 9 and the long arm of chromosome 22 (REF. 4). In this translocation, a large portion of chromosome 22 moved to chromosome 9, and it was assumed that a very small portion of chromosome 9 also moved to chromosome 22. As a consequence, the Ph chromosome was much smaller than the normal chromosome 22 (BOX 1).

Chromosome 9. The next step, which was to clone the translocation breakpoints, occurred a decade later and began to reveal how these chromosomal rearrangements caused leukaemia. c-ABL, the human cellular homologue of the transforming sequence of Abelson murine leukaemia virus (A-MuL V), was known to be located on chromosome 9. In 1982, Dutch researchers investigated whether *c-ABL* was affected by the CML-associated translocation. They hybridized human and viral *ABL* probes to DNA blots of SOMATIC CELL HYBRIDS that contained only the Ph chromosome, and observed that the probe hybridized with the Ph chromosome, but not the $9q^+$ derivative of the translocation[5]. From this, the authors concluded that in CML cells,

Timeline | **History of the study of chromosome translocations in cancer**



ABL sequences are translocated from chromosome 9 to chromosome 22. This finding was the first direct demonstration of a reciprocal exchange between the two chromosomes, and it indicated that *ABL* is involved in the generation of CML[5]. In 1983, Nora Heisterkamp showed that the *ABL* locus was adjacent to the breakpoint. With the help of colleagues, she cloned translocation-associated sequences from both chromosomes 9 (*ABL*) and 22 (REF. 6).

Chromosome 22. In 1984, John Groffen and colleagues examined DNA samples from 19 CML patients for rearrangements on chromosome 22 using Ph translocation breakpoint probes[7]. They found that the Ph chromosome breaks usually occurred within a 5.8-kb region, which they named the 'breakpoint cluster region' (BCR)[7]. This eventually became the name of the chromosome 22 gene that was found to be disrupted by the translocation. Analysis of mRNA from CML patients revealed that the t(9;22) created a fusion between the 5′ part of *BCR* and the 3′ part of *ABL*[8]. The portion of the human *ABL* gene that was contained in the fusion RNA encompassed the coding region, which is homologous to the mouse leukaemia-associated *v-Abl* gene. Later studies showed that the t(9;22)/*BCR–ABL* fusion was essential for the development of CML[9].

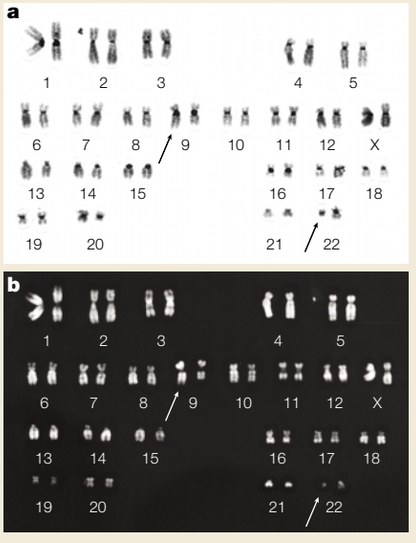
Although the Ph chromosome was initially only associated with CML, lymphocytes from patients with acute lymphoblastic leukaemia (ALL), especially adults, were found to have a similar translocation[10]. The ALL-associated *BCR* breakpoint is different, however, from the one associated with CML. In ALL, the translocation usually occurs in the first intron of *BCR*, resulting in a much smaller portion becoming fused to exon 2 of *ABL*[11].

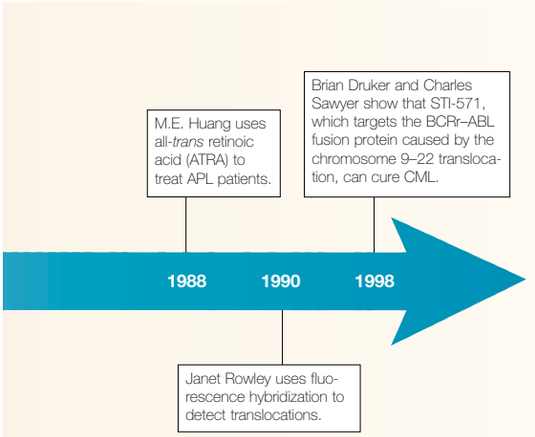
The murine *Abl* gene was well studied and was known to be a tyrosine kinase[12]. In 1984, CML cells were shown to express an altered form of c-ABL with tyrosine kinase activity, indicating a mechanism of action for this oncogene[13]. This activity was greater in Ph-positive ALL cells than in CML cells, and correlated with the fact that ALL is the more aggressive form of leukaemia. But, the reason why the inclusion of a smaller segment of BCR in the fusion protein would increase kinase activity is still unknown.

Analysis of mice receiving bone marrow cells infected with a retrovirus that encodes BCR–ABL showed that this fusion protein was sufficient to cause a myeloproliferative syndrome closely resembling the chronic phase of CML[14]. This is not, however, the only genetic change associated with CML[15], but the basic research that identified this cancer-causing fusion protein as a tyrosine kinase that is

Box 1 | **Early cytogenetic analysis**

In the 1950s and 1960s, chromosomes were studied using Giemsa or Wright stains. With these techniques, chromosomes could be counted accurately and grouped together on the basis of similar size and shape, but they could not be distinguished within morphologically similar groups. In the 1970s, the development of chromosome banding allowed the precise identification of each chromosome and parts of chromosomes. There are several different banding techniques. a | The most commonly used is Giemsa banding (G-banding). G-banding requires pretreatment of cells with trypsin or heat, which removes proteins from chromatin. b | Chromosomes can also be stained with quinacrine mustard (Q-banding). Quinacrine binds preferentially to G+C-rich DNA, which is concentrated in dense chromosome bands that do not contain many genes. Q-banding does not require any type of pretreatment. After chromosomes are stained, they are examined under ultraviolet light and photographed. Individual chromosomes in photographs are cut out and rearranged by chromosome number. Arrows indicate the chromosomes 9 and 22 (Ph) affected by the translocation in CML patients.





specifically expressed by cancer cells made it an attractive therapeutic target. The development of the kinase inhibitor STI-571 almost two decades later has confirmed the wisdom of identifying oncogenes and searching for inhibitors. STI-571 has transformed CML therapy, and might also be useful in treating ALL when combined with other drugs[16].

The Philadelphia story is a scientific success story that began with the initial observation of a chromosome abnormality and its identification as a translocation. This led to the molecular analysis of the genes involved, to the functional characterization of the genes and to the detection of their altered function due to the translocation, and finally to a drug that specifically targets the defective gene product. Hopefully, this model can be followed for the dozens of other translocations that are associated with human leukaemia, lymphoma, sarcomas and some benign tumours (ONLINE TABLE 1).

First genetically defined translocation

Although the Philadelphia chromosome was one of the first translocations to be discovered, the genes involved in the translocation that causes Burkitt's lymphoma were the first to be molecularly characterized. In 1976, Lore Zech and colleagues analysed karyotypes of cells from Burkitt's lymphoma patients, and observed that they contained an extra band at the distal region of the long arm of chromosome 14, whereas the distal region at the long arm of chromosome 8 was missing[17]. They suggested a translocation between chromosomes 8 and 14. It was not until 1982 that Carlo Croce and Bob Gallo showed that the human *MYC* oncogene was located on the region of chromosome 8 and was affected by the translocation[18]. This was the first oncogene cloned at a translocation site. Simultaneously, Phil Leder's group[19] showed that *MYC* was translocated into the 5′ region of the immunoglobulin heavy chain (*IGH*) gene. This translocation, however, did not create a fusion protein, in the same way that the Philadelphia chromosome does. Instead, the translocation juxtaposes the *IGH* promoter region with the *MYC* coding sequences, resulting in abnormal timing and levels of *MYC* expression[20]. This translocation is the most important component of the malignant transformation[21].

Interestingly, other lymphoid cancer-associated translocations also involve immune receptor genes, such as the 14;18 translocation, which is associated with follicular small cleaved-cell lymphoma[22]. This translocation juxtaposes the promoter region of *IGH* with the coding region of the anti-apoptotic protein *BCL2* on chromosome 18 (REF. 23). The anti-apoptotic function of BCL2 was later identified by David Vaux and colleagues[24], launching an enormous new field of cell biological and medical research. Malignant transformations can therefore be induced either by the juxtaposition of a coding region from one gene with the promoter of another gene, or by fusion of two coding regions to create a new, chimeric gene that encodes a fusion protein (FIG. 1). Translocations that cause formation of a fusion protein are the most commonly reported, as they are associated not only with CML, but also with many acute leukaemias and sarcomas (ONLINE TABLE 1).

The impact of molecular biology

The association of particular chromosome translocations with subtypes of leukaemia and lymphoma helped to persuade haematologists and pathologists that chromosome abnormalities, especially translocations, were a crucial aetiological component of these diseases. As more of the genes identified at translocation breakpoints were found to be oncogenes, molecular biologists began to study uncloned chromosome translocations, hoping to identify new cancer-related genes. The cloning of translocation breakpoints has proved to be one of the most efficient ways of identifying new genes that are involved in regulating cell growth and inducing malignant transformation (TABLE 1). For example, the discovery of the AML-associated 8;21 translocation (the first translocation identified)[25] led to the identification of the gene that encodes the haematopoietic transcription factor *AML1* on chromosome 21 (REF. 26). AML1, also known as core binding factor A2 (CBFA2 or RUNX1), binds DNA and heterodimerizes with core binding factor B (CBFB), forming a stable complex that binds DNA more tightly[27]. The gene that encodes CBFB is located at 16q22 and is disrupted by the inv(16) chromosome abnormality[28], which is associated with another type of acute myelomonocytic leukaemia (AML-oM4E)[29]. *CBFA* and *B* are now implicated in about 30% of all acute leukaemias.

Over time, the perception of cytogenetics finally changed from the view that the field was an esoteric backwater with relatively little medical relevance to the realization that it is one of the principal tools for identifying genes involved in malignant transformation. In fact, leukaemia and lymphoma are now the most extensively characterized human malignant diseases[9]. All of the present evidence points to the fact that changes in gene function caused by translocations are crucial events in malignant transformation. We have identified almost 50 translocations that occur in over 1% of leukaemias, lymphomas or other solid tumours (BOX 2), and the genes affected by almost all of these common translocations have been cloned.

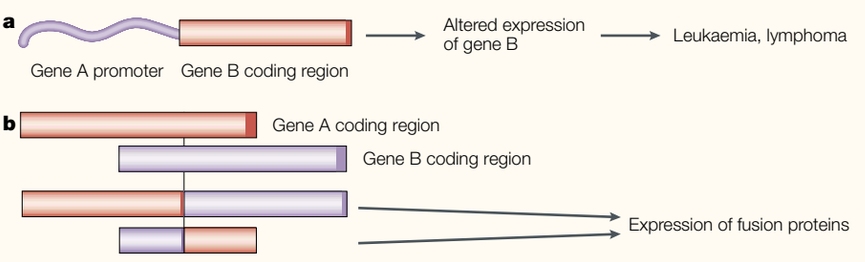


Figure 1 | **The consequences of recurring chromosome translocations. a** | In some lymphomas and leukaemias, chromosome translocations lead to the juxtaposition of promoter/enhancer elements from one gene (gene A, purple) with the intact coding region of another gene (gene B, red). **b** | By contrast, translocations seen in CML and many of the acute leukaemias result in recombination of the coding regions of two different genes. This results in a fusion protein that might have a new function. This is the case for the BCR–ABL fusion protein that is encoded by the Philadelphia chromosome.

Table 1 | **Translocation-disrupted genes**

Class	Gene
Signal transducers	
Tyrosine kinases	*ABL*, *ALK*, *JAK2*, *LCK*, *PDGFRB*
Serine kinases	*BCR*
Surface receptors	*FGFR3*, *TAN1*
Growth factor	*IL3*
DNA-binding factors	
Homeobox	*HOX11*, *HOXA9, HOXD13*, *PBX1*, *PML*, *PMX1*
Helix–loop–helix	*LYL1*, *MYC*, *TAL1*, *TAL2*, *TCF3*
ETS factors	*ERG*, *ETV6*, *FLI1*, *MN1*
Forkhead	*AF6q21*, *AFX*, *FKHR*
Zinc finger	*BCL6*, *ETO*, *EVI1*, *MLL*, *MOZ*, *PLZF*, *PML1*, *RARA*,
LIM	*LMO1*, *LMO2*
Leucine zipper	*AF10*, *AF17*
Other	*AF4*, *AF9*, *CBP/p300*, *DEK*, *E2F*, *ENL*, *LYT10*, *RUNX1*
Other	
Septins	*CDC10rel*, *MSF*
Nucleoporins	*NUP98*, *NUP214*
Transcriptional modulators	*BCL3*, *CBFB*, *ELL*, *NFKB2*
Anti-apoptosis	*AP12*, *BCL2*
RNA binding	*EWS*, *FUS*, *OTT*, *TLS/FUS*

However, we still do not understand the causes of chromosome translocations. Certainly some of them happen just by chance. There is also evidence from lymphoid cells that some translocations occur due to an inappropriate use of DNA recombination mechanisms[30,31]. During T-cell and B-cell development, the genes that encode the immunoglobulin and the T-cell receptors undergo rearrangements. Enzymes that control recombination of these genes recognize signal sequences that activate recombination. Some of the genes involved in translocations share the same signal sequences, and the recombinase machinery might erroneously use these signal sequences to recombine immune receptors with these other genes[30]. This has been reported, for example, for the *TCRA* and *HOX11* genes that are affected by the 10;14 translocation, which leads to T-cell ALL[32]. *TCRA* is the T-cell-receptor-α gene on chromosome 14, and *HOX11* is a member of the homeobox family and is located on chromosome 10. Several studies have indicated that ALU sequences, a family of A+T-rich repeat sequences interspersed frequently throughout the genome, are involved in translocations[33]. The sequences have sufficient homology to pair, which leads to non-homologous recombination. Other studies report that TOPOISOMERASE II cleavage sites and DNASE I HYPERSENSITIVE SITES might be involved in recombination[34]. The precise mechanisms that underlie most cancer-causing translocations, however, have not yet been determined[35].

Box 2 | **How many cancer-associated translocations are there?**

We do not have an accurate number, but the chromosome abnormalities that are present in at least several patients (and are therefore considered to be recurring abnormalities) are included in a catalogue of cancer chromosome abnormalities[44]. The largest number of chromosomal aberrations have been associated with haematological disorders, but many have also been associated with mesenchymal and epithelial tumours. This catalogue began as a journal article, became a printed catalogue and now is available online (see online links box). The catalogue is maintained by the Mitelman group in Sweden, as well as the National Cancer Institute[41]. This database is important because a cytogeneticist can refer to it to determine whether the abnormalities seen in a patient are unique or have been previously reported, and to learn about the clinical features and outcome. A molecular geneticist interested in cloning a particular breakpoint can also use the database to find appropriate patients and material for genetic analysis.

Application to clinical medicine

As more leukaemia patients underwent cytogenetic analysis, clinicians found that the chromosome abnormalities were useful prognostic indicators[36,37] (BOX 2). The development of DNA probes that recognize translocation products has had an important impact on the field of pathology, because assays done with these probes do not require dividing cells, which are necessary for standard cytogenetic analysis. Chromosomal translocations can now be identified using fluorescence *in situ* hybridization (FISH) of cytologic preparations, or through Southern blot analysis. Translocation sequences can also be detected using reverse transcriptase polymerase chain reaction (RT–PCR) and MULTIPLEX RT–PCR, which allows a sample to be screened for the presence of different translocations in parallel.

Cytogeneticists have also created fluorescence probes that hybridize to whole chromosomes, to specific portions of chromosomes or to specific genes (FISH). These probes can be used to identify certain parts of chromosomes, such as centromeres, and to count the number of copies of each chromosome within tumour cells. A more recent technique — known as spectral karyotyping (SKY) — can be used to identify individual chromosomes and rearranged chromosomes (FIG. 2). This technique has greatly improved our ability to identify chromosomal abnormalities in cancer cells.

Many clinics now immediately carry out karyotyping on the cells of a leukaemia patient before treatment, as the identification of chromosome aberrations remains the best known way to predict how a patient will progress or respond to treatment. Some acute myelogenous leukaemia (AML)-associated translocations, such as t(8;21), t(15;17), and inversion[16] are associated with a positive response to treatment and long-term survival[38]. Conversely, a few translocations — such as those involving the *MLL* gene on chromosome band 11q23 — are associated with poor prognosis. Similarly, in ALL patients, the presence of t(12;21) indicates a good prognosis, whereas the presence of the Ph chromosome (the 9;22 translocation) indicates that the disease will advance rapidly.

The importance of translocations in the classification of the leukaemias has been underscored by a recent report from the

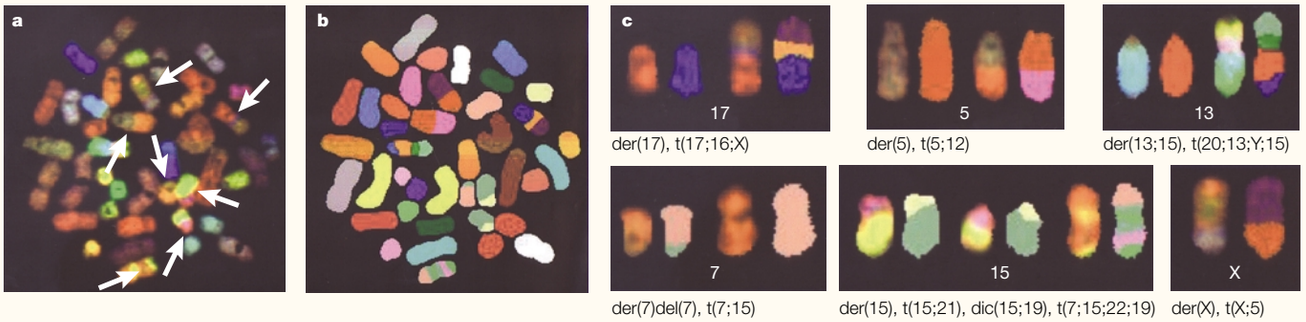


Figure 2 | **Chromosome rearrangements in acute myeloid leukaemia cells.** Metaphase cells from an untreated acute myelogenous leukaemia (AML) patient were analysed using spectral karyotype (SKY) analysis. **a** | The chromosomes were first stained with a mixture of labelled probes specific for different chromosomes. Normal chromosomes are uniform in colour, whereas rearranged chromosomes show two or more colours (arrows). **b** | The spectral pattern of chromosomes has been classified using computer software to identify individual chromosomes. Each chromosome has its own colour code. Several colours on a single chromosome indicate a rearrangement. **c** | Presentation of rearranged chromosomes. Each separate panel shows the spectral and classified images of the normal parent chromosome (left two chromosomes), and the spectral and classified images of the rearranged chromosome (right two chromosomes). The analysis of each chromosome type is listed below, including the chromosome that the rearrangement is derived from (der). In this cell, rearrangements are caused by translocations (t), deletions (del), or dicentric chromosomes (dic). For example, for chromosome 13 (upper right panel), the rearrangements include pieces of chromosome 15, the Y chromosome, chromosome 13 and chromosome 20, from the top to bottom. There are at least 30 separate rearrangements in this cell. Each is not necessarily associated with a cancer.

World Health Organization[9], in which some of the leukaemia categories are identified solely by cytogenetics. Cytogenetic characterization has therefore replaced morphological analysis in the classification of some leukaemias[9]. Translocation type is crucial in determining the most appropriate therapy. For example, an acute promyelocytic leukaemia patient that carryies the t(15;17) is likely to respond to therapy with all-*trans* retinoic acid[39], whereas cells from a CML patient that carries t(9;22) are likely to express the BCR–ABL fusion protein, and can be treated with STI-571 (REF. 16). Cytogenetics can also be used to monitor the response of a patient to therapy. REAL-TIME RT–PCR can be used throughout a patient's treatment programme to monitor the proportion of leukaemic cells that still carry a translocation-induced fusion mRNA.

Malignancy is a multistep process and translocations by themselves are probably, at least in general, not sufficient to induce a fully malignant phenotype. AML patients who carry t(8;21) can remain in complete remission (off treatment) for more than 8 years, even though their peripheral blood still contains *AML–ETO*$^+$ cells[40]. In addition, there are several studies that report the detection of chromosome translocations in cells taken from healthy individuals[41]. There have not been any known follow-up studies of these individuals, however, to determine whether these cells ever became malignant. But together, these data provide evidence that the presence of a translocation is not in itself sufficient for a fully malignant phenotype. Nevertheless, the fact that STI-571 is an effective CML therapy would argue that, even if it is not sufficient, the *BCR–ABL* fusion is necessary for the malignant phenotype.

Glossary

DICENTRIC CHROMOSOME
A chromosome that has two centromeres, formed by breakage and reunion of two chromosomes.

DNASE I HYPERSENSITIVE SITE
DNA sites that are open and accessible to cleavage by DNA-specific enzymes.

MULTIPLEX RT–PCR
Primers for several mRNAs are used in a single RT–PCR reaction, allowing amplification of many (6 –12) separate RNA templates. This technique can be used to screen cells for several translocations at once.

REAL-TIME RT–PCR
RT–PCR using a fluorescent probe that contains a 5′-fluorescent label and 3′-quencher dye. As reverse transcription occurs, the 5′-reporter dye is released and the level of fluorescence emission can be measured as the reaction is proceeding. This technique can be used throughout a patient's treatment programme to monitor the proportion of leukaemic cells that still carry a translocation-induced fusion mRNA.

RT–PCR
(Reverse transcriptase polymerase chain reaction). This technique can be used to amplify cDNA from an mRNA template, using sequence-specific primers. Primers for fusion mRNAs created by known chromosome translocations can be used to identify cancer cells.

RING CHROMOSOME
Two breaks occur in the same chromosome, on opposite sides of the centromere. In these chromosomes, the ends of the centric fragment fuse.

SOMATIC CELL HYBRID
Fusion of cells from two species, often rodent and human. This causes loss of chromosomes, reducing the number of chromosomes from one species. These were important early tools used for mapping the location of genes to chromosomes.

TOPOISOMERASE II
An enzyme that binds to double-stranded DNA, cleaves both strands, passes one strand through the other to unwind the DNA and then relegates the broken ends.

Future directions

The karyotypes of malignant cells have provided us with a wealth of information about the genetic and molecular basis of cancer. We have been successful in identifying genes that become disrupted by chromosome translocations, but considerably less successful in identifying the genes that are lost in chromosome deletions. For example, a deletion in the long arm of chromosome 5 is associated with AML — especially in individuals who have received previous mutagenic therapy[42]. Although this deletion has been studied for almost two decades[43] and occurs in a sequenced, gene-rich region, the gene or genes that are disrupted by this deletion are still unknown. Chromosome deletions are a particularly interesting area of genetic research, as they are frequently accompanied by translocations or other complex chromosome abnormalities. We have also been unsuccessful in identifying the genes that are affected by chromosome amplification, except for cases in which the genes are present in dozens of copies.

It is important to gain a better understanding of the full genetic and molecular effects of chromosome rearrangements, as this is one of the best routes to developing cancer-specific designer drugs. One of the lessons learned from the STI-571 story is that going from genotype to therapy requires a diverse group of scientists, along with the support of industrial research. Although the financial rewards for industry might not be great, the important thing — the therapeutic benefits – are immeasurable.

Janet D. Rowley is at the Section of Hematology/Oncology, Department of Medicine, University of Chicago Medical Center, 5841 South Maryland Avenue, MC 2115, Chicago, Illinois 60637, USA.
e-mail: jrowley@medicine.bsd.uchicago.edu

1. Boveri, T. in *Zur Frage der Entstehung maligner Tumoren* (Gustav Fischer, Jena, 1914).
2. Levan, A. Some current problems of cancer cytogenetics. *Hereditas* **57**, 343–355 (1967).
3. Nowell, P. & Hungerford, D. A minute chromosome in human granulocytic leukemia. *Science* **132**, 1497 (1960).
4. Rowley, J. D. A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature* **243**, 290–293 (1973).
5. de Klein, A. A. Cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukemia. *Nature* **300**, 765–767 (1982).
6. Heisterkamp, N. *et al*. Localization of the c-ABL oncogene adjacent to a translocation breakpoint in chronic myelocytic leukemia. *Nature* **306**, 239–242 (1983).
7. Groffen, J. *et al*. Philadelphia chromosomal breakpoints are clustered within a limited region, *BCR*, on chromosome 22. *Cell* **36**, 93–99 (1984).
8. Shtivelman, E., Lifschitz, B., Gale, R. P. & Canaani, E. Fused transcript of *ABL* and *BCR* genes in chronic myelogenous leukaemia. *Nature* **315**, 550–554 (1985).
9. Jaffe, E. S., Harris, N. L., Stein, H. & Vardiman, J. W. (eds) *World Health Organization Classification of Tumours, Pathology and Genetics: Tumours of the Hematopoietic and Lymphoid Tissues* (IARC, Lyon, 2001).
10. Berger, R., Chen, S. J. & Chen, Z. Philadelphia-positive acute leukemia. Cytogenetic and molecular aspects. *Cancer Genet. Cytogenet.* **44**, 143–152 (1990).
11. Hermans, A. *et al.* Unique fusion of *BCR* and c-*ABL* genes in Philadelphia chromosome positive acute lymphoblastic leukemia. *Cell* **64**, 343 (1987).
12. Witte, O. N., Dasgupta, A. & Baltimore, D. Abelson murine leukemia virus protein is phosphorylated *in vitro* to form phosphotyrosine. *Nature* **281**, 396–398 (1980).
13. Konopka, J. B., Watanabe, S. M. & Witte, O. N. An alteration of the human c-ABL protein in K562 leukemia cells unmasks associated tyrosine kinase activity. *Cell* **37**, 1035–1042 (1984).
14. Daley, G. Q., Van Etten, R. A. & Baltimore, D. Induction of chronic myelogenous leukemia in mice by the p210 *BCR/ABL* gene of the Philadelphia chromosome. *Science* **247**, 824 (1990).
15. Fialkow, P. J. in *Genes and Cancer* (eds Bishop, J. M., Rowley, J. D. & Greaves, M.) 215–226 (Alan R. Liss, New York, 1984).
16. Druker, B. J. *et al.* Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N. Engl. J. Med*. **344**, 1038–1042 (2001).
17. Zech, L., Haglund, U., Nilsson, K. & Klein, G. Characteristic chromosomal abnormalities in biopsies and lymphoid-cell lines from patients with Burkitt and non-Burkitt lymphomas. *Int. J. Cancer* **17**, 47–56 (1976).
18. Dalla-Favera, R. *et al*. Human c-*MYC* onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. *Proc. Natl Acad. Sci. USA* **79**, 7824–7827 (1982).
19. Taub, R. *et al*. 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**, 7837–7841 (1982).
20. ar-Rushdi, A. *et al*. Differential expression of the translocated and the untranslocated c-*MYC* oncogene in Burkitt lymphoma. *Science* **222**, 390–393 (1983).
21. Adams, J. M. *et al.* The c–*Myc* oncogene driven by immunoglobulin enhancers induces lymphoid malignancy in transgenic mice. *Nature* **318**, 6046 (1985).
22. Fukuhara, S., Rowley, J. D., Variakojis, D. & Golomb, H. M. Chromosome abnormalities in poorly differentiated lymphocytic leukemia. *Cancer Res.* **39**, 3119–3128 (1979).
23. Tsujimoto, Y., Finger, L. R., Yunis, J., Nowell, P. C. & Croce, C. M. Cloning of the chromosome breakpoint of neoplastic B cells with the t(14;18) chromosome translocation. *Science* **266**, 1097–1099 (1984).
24. Vaux, D. L., Cory, S. & Adams, J. M. *Bcl-2* gene promotes haemopoietic cell survival and cooperates with c-Myc to immortalize pre-B cells. *Nature* **335**, 440–442 (1988).
25. Rowley, J. D. Identification of a translocation with quinacrine fluorescence in a patient with acute leukemia. *Ann. Genet.* **16**, 109–112 (1973).
26. Miyoshi, H. *et al.* The t(8;21) breakpoints on chromosome 21 in acute myeloid leukemia clustered within a limited region of a novel gene, *AML1*. *Proc. Natl Acad. Sci. USA* **88**, 10431 (1991).
27. Wang, Q. *et al.* The CBFβ subunit is essential for CBFα2 (AML1) function *in vivo*. *Cell* **87**, 697–708 (1996).
28. Le Beau, M. M. *et al*. Association of inv(16)(p13q22) with abnormal marrow eosinophils in acute myelomonocytic leukemia: a unique cytogenetic-clinicopathologic association. *N. Engl. J. Med.* **309**, 630–636 (1983).
29. Liu, P. *et al.* Fusion between transcription factor CBF?/PEBP2? and ? myosin heavy chain in acute myeloid leukemia. *Science* **261**, 1041–1044 (1993).
30. Finger, L. R., Harvey, R. C., Moore, R. C., Showe, L. C. & Croce, C. M. A common mechanism of chromosomal translocation in T and B cell neoplasia. *Science* **234**, 982–985 (1986).
31. Rabbitts, T. H., Boehm, T. & Mengle-Gaw, L. Chromosomal abnormalities in lymphoid tumors: mechanism and role in tumor pathogenesis. *Trends Genet.* **4**, 300 (1988).
32. Hatano, M., Roberts, C. W., Minden, M., Crist, W. M. & Korsmeyer, S. J. Deregulation of a homeobox gene, HOX11, by the t(10;14) in the T cell leukemia. *Science* **253**, 79 (1991).
33. Schichman, S., Canaani, E. & Croce, C. M. Self-fusion of the *ALL-1* gene: a new genetic mechanism for acute leukemia. *J. Am. Med. Assoc.* **273**, 571–576 (1995).
34. Strissel, P. A. *et al*. DNA structural properties of *AF9* are similar to *MLL* and could act as recombination hot spots resulting in *MLL/AF9* translocations and leukemogenesis. *Hum. Mol. Genet.* **9**, 1671–1679 (2000).
35. Stanulla, M., Wang, J., Chervinsky, D. S., Thandla, S. & Aplan, P. D. DNA cleavage within the MLL breakpoint cluster region is a specific event which occurs as part of higher-order chromatin fragmentation during the initial stages of apoptosis. *Mol. Cell. Biol.* **17**, 4070–4079 (1997).
36. Mitelman, F. The Third International Workshop on Chromosomes in Leukemia. Lund, Sweden, July 21–25, 1980. Introduction. *Cancer Genet. Cytogenet.* **4**, 96–98 (1981).
37. Bloomfield, C. D., Goldman, A., Hossfeld D. & de la Chapelle, A. Fourth International Workshop on Chromosomes in Leukemia 1982: clinical significance of chromosomal abnormalities in acute nonlymphoblastic leukemia. *Cancer Genet. Cytogenet.* **11**, 332–350 (1984).
38. Grimwade, D. *et al.* The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. *Blood* **92**, 2322–2333 (1998).
39. Huang, M. E. *et al.* Use of all-*trans* retinoic acid in the treatment of acute promyelocytic leukemia. *Blood* **72**, 567–572 (1988).
40. Nucifora, G. & Rowley, J. D. AML1 and the 8;21 and 3;21 translocations in acute and chronic myeloid leukemia. *Blood* **86**,1–14 (1995).
41. Uckun, F. M. *et al.* Clinical significance of MLL-AF4 fusion transcript expression in the absence of a cytogenetically detectable t(4;11)(q21;q23) chromosomal translocation. *Blood* **92**, 810–821 (1998).
42. Rowley, J. D., Golomb, H. M. & Vardiman, J. W. Nonrandom chromosomal abnormalities in acute nonlymphocytic leukemia in patients treated for Hodgkin's disease and non-Hodgkin lymphomas. *Blood* **50**, 759–770 (1977).
43. Zhao, N. *et al.* Molecular delineation of the smallest commonly deleted region of chromosome 5 in malignant myeloid diseases to 1–1.5 Mb and preparation of a PAC-based physical map. *Proc. Natl Acad. Sci. USA* **94**, 6948–6953 (1997).
44. Mitelman, F. *Catalog of Chromosome Aberrations in Cancer* 5th edn (Wiley–Liss, New York, 1994).
45. Olney, H.J., Gozzetti, A., & Rowley, J.D. in *Hematology of Infancy and Childhood* 6th edn (eds. Nathan, D., Orkin, S., Look, T. & Ginsburg, D. (WB Saunders, Philadelphia, 2002, in the press).
46. Chaganti, R., Nanjangud, G., Schmidt, H. & Teruya-Feldstein, J. Recurring chromosomal abnormalities in non-Hodgkin's lymphoma: biologic and clinical significance. *Sem. Hematol.* **37**, 396–411 (2000).

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