Oncogene chromosome breakpoints and *Alu* sequences

IT has recently been shown[1,2] that the human leukaemia-associated 'Philadelphia chromosome' results from a reciprocal translocation which fuses the c-*abl* gene on chromosome 9 with the *bcr* gene on chromosome 22. However, the exact position of the breakpoint in one of the recently published sequences[1] needs clarification, because repeated sequences of the *Alu* dispersed repeat family[3] are present. This breakpoint, like some others, may have resulted from illegitimate recombination within an *Alu* sequence.

In one of the cases reported by Heisterkamp *et al.*[1] (0319129), the authors noted homology to *Alu*; an *Alu* unit on chromosome 9 has recombined with a partly similar but misaligned sequence on chromosome 22 (see Fig. 1). In the other case (02120185), the presence of *Alu* sequences was overlooked and makes the identification of the breakpoint ambiguous. As shown in Fig. 1, the translocation chromosome (9q+) again has an *Alu* unit recombined with a non-homologous sequence from chromosome 22. This *Alu* unit lacks the first 103 nucleotides of the standard *Alu* sequence, and its truncated 5′ end is joined to the chromosome 22 sequence with a 2-nucleotide overlap (nucleotides 109–110 of Fig. 3*b* of ref. 1; vertical bar in our Fig. 1).

The data presented do not make it clear whether this is the actual 9;22 junction. The 'chromosome 9' sequence aligned by the authors appears to be a different *Alu* sequence—in fact, two 3′-half-*Alu* sequences joined by a long A-rich tract—with numerous (13/81) differences from the 9q+ *Alu* sequence. If the latter is indeed from chromosome 9, it is probably derived from a different *Alu* unit, which could be located in chromosome 9 clones by identifying unique chromosome 9 sequences at the other end of the *Alu* sequence. Alternatively, it may be a 5′-truncated *Alu* unit inserted into chromosome 22 sequences on 9q+; this would be an unlikely coincidence, but 5′-truncated insertions do occur[4].

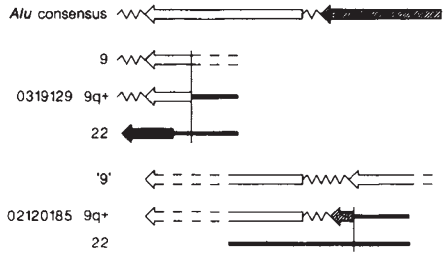

Fig. 1 Disposition of *Alu* sequences in the sequences of Heisterkamp *et al.*[1]. In each case the *Alu* (+)-strand is homologous to the (−)-strand of the published sequences. The 300-nucleotide *Alu* consensus (top line)[3] consists of two homologous halves, each followed by an A-rich tract which is indicated by zigzags. The filled box indicates a partly *Alu*-related sequence noted by Heisterkamp *et al.*[1].

The fact that one and probably both of the 9;22 translocations occurred within *Alu* sequences is interesting in itself. Four separate thalassaemias have been caused by illegitimate recombination within *Alu* sequences[5]; so has one case of familial hypercholesterolaemia[6]. All these had breakpoints at different points in the *Alu* sequence. Because *Alu* sequences constitute 3–5% of the human genome, these occurrences could be coincidental[5], but it is possible that *Alu* sequences are hot spots for illegitimate recombination.

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HEISTERKAMP AND GROFFEN REPLY—We agree with Rogers that the positioning of the breakpoint in chronic myelogenous leukaemia (CML) patient 02120185 is subject to discussion. Although we discussed some aspects of the consequences of the Ph′ translocation in this patient[1], we would like to elaborate on this issue. We have shown previously[2] that the 9q+ fragment of this patient represents a chromosome 9;22 chimaeric DNA fragment. The normal chromosome 9 DNA sequences were subsequently isolated using the chromosome 9 part of the 9q+ as a probe, thus demonstrating that the chromosome 9 and 9q+ sequences must form a set. Subsequently, we have localized the 'breakpoint' on the normal chromosome 9 fragment by comparative restriction enzyme analysis of the normal chromosome 9 and 9q+ fragments. On a nucleotide level, the situation is less clear. As we have indicated, 13 nucleotides within an 81-base-pair (bp) stretch are different between the 9 and 9q+ chromosome; moreover, 27 bp on the 9q+ chromosome do not originate from the chromosome 22 or chromosome 9 sequences shown.

Although the sequences shown[1] must represent the actual $9q^+$ sequences present in patient 02120185, we cannot with certainty define the mechanism by which this configuration was attained; we favour the explanation that on translocation of the chromosome 22 sequences to chromosome 9, the resulting 9q+ chromosome was unstable, and a deletion, probably between *Alu* sequences, occurred. The boxed 9q+ sequences would then represent the original 9q+ sequences while sequences more to the 5′ would originate from sequences located more towards the centromere of the breakpoint on chromosome 9. Nonetheless, we cannot exclude the possibility suggested by Rogers that a 5′-truncated *Alu* unit was inserted into the chromosome 22 sequences on the 9q+ chromosome.

It is also noteworthy that part of the *Alu* sequences on chromosome 9 of 02120185 (14 bp 3′ of the breakpoint) are homologous with the *Alu* sequences of chromosome 9 in patient 0319129: of 42 nucleotides in 02120185, 36 can be found surrounding the breakpoint in patient 0319129. This suggests that the breakpoints on chromosome 9 fall within similar types of *Alu* repeat sequences. However, on chromosome 22, breakpoints and *Alu* repeats do not seem to coincide; although *Alu* sequences can be found in the sequences around the breakpoint on chromosome 22 in patient 0319129, similar sequences seem to be absent in patient 02120185. Moreover, regions of *bcr* containing numerous breakpoints for different CML patients have been used as repeat-free probes[2] in Southern hybridizations, indicating that these regions lack *Alu* repetitive sequences. Therefore, *Alu* sequences may be hot spots for recombination, but not all illegitimate recombination events in CML seem to occur within repetitive sequences.

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The age of (a tiny part of) the Australian continent

SCHÄRER and Allègre[1], using isotope dilution analysis of single grains and fragments of zircon, recently failed to substantiate a report by Froude *et al.*[2], based on the ion microprobe SHRIMP[3], of zircons older than 4,100 Myr from Mt Narryer, Western Australia. In their discussion, Schärer and Allègre disparaged the ion microprobe results on various grounds, although they did not actually state that they were wrong. Here, we wish to give a simple explanation for Schärer and Allègre's null observation, to correct an evident misreading of Froude *et al.*, and to advise that the ages of the >4,100-Myr-old zircons are unchanged following reanalysis by SHRIMP and that several more such grains have been discovered.

Schärer and Allègre did not discuss the statistical implications of the very low abundance of the >4,100-Myr-old grains (hereafter termed the 'old' grains) found by Froude *et al.*, which was 4 in a total of 102 zircons analysed at that time. Suppose for the moment that this abundance is exactly right, so that the chance of selecting a single young grain will be 0.96; it follows that the chance of selecting 32 young grains in succession, which Schärer