GLOSSARY

TEL-AML1 ALL
A form of acute lymphoblastic leukemia in which the *TEL* and *AML1* genes are fused

ARLTS1
ADP-ribosylation factor-like tumor-suppressor gene 1; now known as *ARL11* (ADP-ribosylation factor-like 11)

to compare the social interactions of children diagnosed with acute lymphoblastic leukemia (ALL) with those of healthy controls. Their findings reinforce the hypothesis that exposure to common infections during infancy reduces the risk of developing childhood leukemia.

Between 1991 and 1996, this large, multicenter study recruited cases and controls aged 2–14 years on a 1:2 ratio, matched for age, sex, and area of residence. Parents of eligible cases ($n = 3,140$) and controls ($n = 6,305$) were questioned on the nature and frequency of their child's social contact with other children outside the family. Three levels of interaction were defined; social activity—contact with other children at least once a week; day care—attendance at a nursery at least once a week; and formal day care—attendance at a nursery with at least four other children at least two half-days each week. Analysis was performed for combined ALL malignancies, and individually for B-cell precursor common ALL, hyperploid ALL, TEL-AML1 ALL, and non-ALL cancers.

Social interaction, on all levels, significantly reduced the risk of ALL malignancies ($P < 0.001$) and this relationship persisted, with a more marked effect for increasing levels of social activity, for each class of ALL. Children in the formal day care category showed the most significant risk reduction ($P = 0.02$), an effect further enhanced if formal day care was attended before the age of 3 months ($P = 0.007$). The authors conclude that regular social activity, particularly formal day care, during the early months of life exerts a protective effect against childhood ALL.

Original article Gilham C *et al.* (2005) Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study. *BMJ* [doi:10.1136/bmj.38428.521042.8F]

Chemotherapy-related acute promyelocytic leukemia: role of topoisomerase II

Development of acute myeloid leukemia (AML) is often associated with reciprocal balanced chromosomal translocations. Chemotherapeutic agents that poison topoisomerase II—for example, mitoxantrone—have been implicated in this process. An international study by Mistry *et al.* has now shown that topoisomerase II is directly involved in formation of the t(15;17) chromosomal translocation, in patients with chemotherapy-related acute promyelocytic leukemia (APL)—one of the commonest forms of AML. The t(15;17) is the most frequent translocation in APL, and disrupts the *PML* and *RARA* genes giving rise to the PML-RARα oncoprotein.

The study included six patients who developed APL following mitoxantrone-based treatment for breast carcinoma or multiple sclerosis. The genomic breakpoints in *PML* and *RARA* were characterized using long-range polymerase chain reaction and DNA sequence analysis. In four of the patients, the translocation breakpoints were tightly clustered in an 8-base pair region of intron 6 of the *PML* gene; this clustering was unlikely to have arisen by chance and so was suggestive of a 'hot spot' of DNA damage.

Next, the normal homologue of this translocation breakpoint hot spot was analyzed using functional *in vitro* topoisomerase II cleavage assays. This revealed that topoisomerase II-mediated cleavage at this site was enhanced 9-fold by exposure to mitoxantrone. The corresponding *RARA* breakpoints were also matched to mitoxantrone-induced sites of cleavage by topoisomerase II.

These observations also applied to patients who had been treated with etoposide or doxorubicin, suggesting that treatment with other topoisomerase II poisons can lead to the observed topoisomerase II-mediated cleavage of DNA in therapy-related APL.

Original article Mistry AR *et al.* (2005) DNA topoisomerase II in therapy-related acute promyelocytic leukemia. *N Engl J Med* **352:** 1529–1538

Role of *ARLTS1* in familial cancer

Calin and co-workers have discovered a link between a genetic variant of *ARLTS1* at chromosome 13q14 and the risk of familial cancer. Their study has recently been published in the *New England Journal of Medicine.*

Following the observation that deletions at chromosome 13q14.3 occur in a variety of tumors, the investigators studied the genes in this region and identified *ARLTS1*, a member of the ADP-ribosylation-factor family. Next,