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## CAUSES OF CHILDHOOD CANCER NEWSLETTER

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### Of Mice and Men.

Acquired somatic mutations in exon 2 of the hematopoietic transcription factor GATA-1 have been found in the blasts of children with Down syndrome transient myeloproliferative disorder (TMD) and acute megakaryoblastic leukemia (AMKL). These mutations prevent synthesis of the full-length protein but allow synthesis of its short isoform, GATA-1s. Perhaps surprisingly, mice expressing only GATA-1s have normal adult megakaryopoiesis, platelet formation and erythropoiesis. In a fascinating new report, **Holland LM et al [Nature Genetics, 2006; 38: 807-812]** describe a mutation, 332G→C, in exon 2 of GATA-1 leading to the synthesis of only the short isoform in seven affected males (GATA is on the X chromosome) from 2 generations of a single family. Affected males had macrocytic anemia, normal platelet counts and neutropenia in most cases. Anemia and neutropenia were sufficiently severe to require bone marrow transplantation in two cases. These data show that in contrast to mouse models, GATA-1s is not sufficient to support normal erythropoiesis in humans. None of the cases developed leukemia, showing that this mutation is not leukemogenic in the absence of other cooperating events such as Down syndrome.

COMMENT: This study demonstrates that a small animal model (mouse) does not always reflect accurately what is happening in a large animal model (men). While murine studies are valuable, findings require verification in humans before being accepted as true. The conundrum of the cooperation between trisomy 20, GATA-1 and other possible secondary genetic events remains incompletely explained and future cooperative group epidemiology and biology studies may help unravel this enigma. Stella M. Davies

### Birth weight, leukemia, and mom's highs and lows

High birth weight (> 4000 grams) is becoming an established risk factor for childhood leukemia (both ALL and AML), with the risk estimated to increase by 25-50% in the largest babies. The strongest predictors of high birth weight today are maternal pregnancy body mass index and maternal weight gain during pregnancy. Few epidemiologic studies of birth weight and childhood leukemia have taken these factors into account. In this report by **McLaughlin CC et al [Br J Cancer 2006;**

**94:1738-1744]**, maternal pregnancy weight and weight gain during pregnancy were evaluated in a case-cohort study of childhood leukemia in New York. A total of 916 acute lymphoblastic leukemia (ALL) cases and 154 acute myeloid leukemia (AML) cases diagnosed prior to age 10 years during the period 1985-2001 and born in New York State (excluding New York City) during the period 1978-2001 were included. (New York City was excluded since it contains a separate birth registry that was not available to the authors). Controls (n=9686) were selected from the same birth cohorts during the same time period. Data from the birth certificates used in these analyses included birth weight, sex, race/ethnicity, maternal prepregnancy weight and maternal weight gain during pregnancy (only 1988 forward), maternal diabetes (yes/no), maternal height (only 1993 forward) and maternal age. As expected, high birth weight (3500 g or higher) was associated with an increased risk of leukemia (adjusted Odds Ratio (OR)=1.17, 95% Confidence Interval (CI)=1.01-1.35) compared to birth weight less than 3500 g. Overall, there was a 25% increased risk with each 1kg increase in birth weight, which is similar to other reported studies. Maternal prepregnancy weight was associated with an increased risk of ALL, with a significant test for trend (p=0.03), particularly for those diagnosed less than 5 years of age (p=0.0002). Body mass index classified as overweight or obese (> 25 kg/m<sup>2</sup>) was only able to be calculated on a subset of cases (75%) and controls (81%). However, there was an increased risk of ALL (OR=1.44, 95% CI=1.03-2.01) in children of mother's with high BMI for cases diagnosed less than 5 years of age. Intriguingly, there was an increased risk of ALL among children whose birth weights were discordant with mother's weight. In other words, children without high birth weight (<3500 g) but whose mothers were heavy (80+kg), and children with high birth weight (>= 3500 g), whose mothers were not heavy (<80 kg), appeared to be at the highest risk (OR=1.72, 95% CI=1.16-2.48; OR=1.26; 95% CI=1.01-1.57, respectively). Higher maternal weight gain during pregnancy was also associated with ALL, but there was little evidence of an interaction with maternal weight or birth weight (p=0.14). Maternal diabetes was associated with a nonsignificant increased risk of ALL independent of other factors. For AML, both low and high birth weight was associated with an increased risk, similar to that reported in other studies. For prepregnancy weight 80+ kg, there was an increased risk (OR=2.25, 95% CI=1.18, 2.34), although a test for

trend was not informative. Further, there was evidence of a decreased risk of AML with increasing weight gain during pregnancy. Finally, older maternal age was associated with an increased risk of AML (OR (maternal age 40+ years compared to 20-29 years)=3.68, 95% CI=1.48-7.85) but not ALL (although it appears as though children with Down syndrome were not excluded).

COMMENT: This is a well executed analysis using birth registry data. Importantly, these data are not subject to recall bias. As the authors cautiously note, there are concerns regarding birth certificate data completeness and validity particularly with respect to prepregnancy weight, weight gain during pregnancy, and gestational age. Nevertheless, any misclassification errors would be non-differential. Importantly, this the first study to show a complex relationship with maternal weight, birth weight and risk of childhood ALL. Because mother's prepregnancy weight and weight gain during pregnancy are the strongest predictors of having a high birth weight infant, the finding of an increased risk of childhood ALL for mothers who are not heavy but have a high birth weight child, along with mothers who are heavy but have an average weight child, suggest unique biological processes at work. Julie A. Ross

### MLL and transformation- what's missing

The vast majority of infants with leukemia demonstrate rearrangement of the mixed lineage leukemia (MLL) gene on chromosome band 11q23 with one of over 40 different partner genes (most commonly genes on chromosomes 4, 9, and 19). Secondary acute myeloid leukemias associated with prior exposure to DNA topoisomerase II inhibiting therapies also demonstrate MLL gene rearrangements often with translocation involving chromosomes 9 or 19. Chemotherapy-associated leukemias occur on average 27 months following therapy; infant leukemia arises in utero. Assuming additional mutations occur (a subset of infants have additional FLT3 mutations or other additional chromosomal abnormalities in their leukemia cells), it is important to consider how quickly the disease arises. Unfortunately, animal models have not been informative, since latency periods are protracted for MLL-AF9 and MLL-AF4 knock-in mice. In this report, **Eguchi M et al [Genes, Chromosomes & Cancer 2006; 45:754-760]** hypothesized that limitations of animal model studies include a) a chronicity of exposure that causes the MLL gene rearrangement is missing; and b) a compromised recognition and/or repair of DNA damage due to MLL fusion proteins. The authors tested this hypothesis by using a hormone (4-hydroxy-tamoxifen (4OHT)) that controls expression of the MLL-ENL transcript in mouse progenitor cells. In the absence of 4OHT, the MLL-ENL protein is expressed but inactive, in the presence of 4OHT, the active form of MLL is expressed. The design compared cells in the presence or absence of 4OHT following exposure to VP-16 for 16 hours. After exposure to VP16, many cells with and without active MLL-ENL transcripts had substantial chromosomal damage. Normal cells that experience DNA damage will typically arrest in cycle progression, repair the damage or apoptose. The authors found <1% discernable chromosomal abnormalities detected by FISH in clonogenic cells without active MLL-ENL transcripts. In contrast, 10% of clonogenic cells arising from the activated MLL-ENL line showed chromosome

abnormalities. The authors conclude that cells with active MLL-ENL transcripts that survive exposure to genotoxic levels of VP16 are significantly more likely to carry unrepaired DNA damage than the same cells expressing an inactive form of MLL-ENL. Relevant to infant leukemia, the authors suggest that chronic or intermittent exposure to transplacental exposures that are equivalent to VP16 (i.e., DNA topoisomerase II inhibitors) may also facilitate induction of functional MLL transcripts along with the rapid acquisition of further DNA damage, leading to frank leukemia at or shortly after birth.

COMMENT: This in vitro study provides additional support for the role of DNA topoisomerase II inhibitors in the etiology of leukemia with MLL gene translocations. Notably, the authors suggest that the relatively protracted latencies observed in mouse models that utilize a MLL fusion gene may be due to a lack of genotoxin exposure. It will be important to develop animal model studies that utilize this approach to create testable hypotheses related to DNA topoisomerase II inhibitors and leukemia. Julie A. Ross

### Facial tumors: NOT the devil's advocate

In this report, the authors evaluate the transmission of facial-tumor disease in Tasmanian devils in Australia. Devils, through their very nature, fight and bite each other frequently, often in the facial area. It has been noted that over 50% of the devil population is affected by facial tumors. Unfortunately, this is devastating the population, since the animals affected can ultimately starve due to tumor burden. There is intense interest in determining the mode of transmission of the tumor from one devil to the next. **Pearse and Swift [Nature 2006; 439:549]** recently reported an evaluation of tumors from 11 affected devils. Notably, devils have 14 chromosomes, including the sex chromosomes. All the tumors studied (from 11 different devils) had an identical complex karyotype with only 13 chromosomes, including deletion of both sex chromosomes and chromosomes 2, and 1 chromosome 6. Further, a deletion of the long arm of chromosome 1 and four unidentified marker chromosomes were present. No intermediate stages were found between normal and tumor chromosomes, even in small primary cancers. This implies that no common breakpoint occurs, and thus it is likely that these tumors are being passed by allograft. Further, in one devil, there was a constitutional pericentric inversion of chromosome 5, but this inversion was not found in the facial tumor cells- indicating the tumor did not arise from his own tissue.

COMMENT: This is a fascinating study that implicates transmission of tumor through infection, perpetuated by allografting. Although rare, there are examples where transmission of malignancy occurs through organ transplantation. There are also examples from animals, where sarcoma has been shown to transmit in dogs. In the current report, the authors did not speculate as to how the tumor cells are transmitted, but one would have to assume that these cells are transmitted through saliva. Devils are a genetically fairly closed population with limited genetic diversity and may be unable to mount an immune response to reject allogeneic tumors. Because facial tumors could result in the decimation of the devil population, it is important to determine the natural history of disease in the population and determine whether a vaccine can be developed. Julie A. Ross