Session I Cancer Cytogenetics
Chair, AnnMarie Block, Roswell Park

Testing strategy and clinical implications of Jak2 mutation analysis
S. Kamel-Reid, University of Toronto, Toronto General Hospital

Myeloproliferative disorders (MPDs) are clonal stem cell disorders characterized by the proliferation of myeloid lineages in the bone marrow, due to cytokine hypersensitivity yet virtually normal cell maturation. They have classically included polycythemia vera (PV), essential thromobocythemia (ET), chronic idiopathic myelofibrosis (IMF) and chronic myeloid leukemia or CML. More recently, they have also included hypereosinophilic syndrome (HES), chronic eosinophilic leukemia (CEL) and chronic neutrophilic leukemia (CNL). Classification of MPDs is often difficult, and they can be confused with more benign or reactive conditions. Only CML was associated with a non-random genetic alteration, the BCR-ABL fusion gene, a molecular marker that simplified diagnosis. Recently several different groups have identified a gain of function mutation in MPDs, in the JH2 domain of the Janus Kinase 2 (JAK 2) gene on chromosome 9. This mutation is due to a G to T transversion that results in phenylalanine being substituted for valine at position 617 (V617F) and is thought to participate in the pathogenesis of PV, ET and IMF, although the precise mechanism may not be the same for all three sub-types. We are currently using ARMS to identify this mutation in patients with a referring diagnosis of PV, ET or IMF. This technology will be reviewed as well our algorithm for use of this genetic test. An explanation of the mechanism of action of this mutation, the different subtypes of MPD and their characteristics and the potential clinical utility of this test will also be discussed.

When is an HSR not an HSR
James V. Higgins and Denise Kowalko, Spectrum Health

A patient was referred because of thrombocytopenia. A bone marrow evaluation shows MDS. Our cytogenetic evaluation shows the karyotype 44,XX,del(5q),-11,der(11)t(11;11) and -18 in 13 cells, 6 cells were 46,idem, with a ring chromosome and only 1 was a 46,XX. We will discuss the pathology, the flow cytometry evaluation and the presence of an HSR for the MLL gene site per FISH. We will discuss the prognosis related to the abnormalities.

Detection of two novel variant *TMPRSS2/ERG* fusion transcripts suggests independent genomic alterations may underlie the origin of multi-centric prostate cancer
Maisa Yoshimoto,[1] Anthony M. Joshua,[1,2,3] Susan Chilton-MacNeill,[4] Jane Bayani,[1] Shamini Selvarajah,[1,4] Andrew J. Evans,[1,5] Maria Zielenska[4] and Jeremy A. Squire,[1,2] [1]Applied Molecular Oncology, Ontario Cancer Institute, Princess Margaret Hospital, Toronto, Ontario, Canada; [2]Department of Medical Biophysics, Faculty of Medicine, University of Toronto, Canada; [3]Department of Medical Oncology, Princess Margaret Hospital, Toronto, Ontario, Canada; [4]Department of Pathology and Laboratory Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada; [5]Department of Pathology, Princess Margaret Hospital, Toronto, Ontario, Canada

The recent description of novel recurrent gene fusions in ~80% of prostate Cancer has generated increased interest in the search for new translocations in other epithelial cancers, and also emphasizes the importance of understanding the origins and biological implications of these genomic rearrangements. Analysis of 15 prostate cancers by RT-PCR was used to detect 6 *ERG*-related gene fusion transcripts with *TMPRSS2*. Break-apart three-color FISH confirmed that a deletion between *TMPRSS2* and *ERG* on chromosome 21 was associated with gene fusions. One multicentric carcinoma exhibited two distinct previously undescribed fusion transcripts,

implying independent clonal origins and suggests that the mechanism responsible for the translocations is common in the multifocal nature of prostatic carcinogenesis.

CML : What the clinician needs and wants to know in 2006

Harold Olney, CHUM Notre Dame, Montreal

Chronic myeloid leukemia (CML) is a proliferative clonal disorder of hematopoietic stem cells that results primarily in the expansion of mature myeloid cells. Until the 1980s, CML was invariably a fatal disease. In that decade, the coming of age of bone marrow transplantation and the recognition of the activity of interferon alpha permitted a minority of patients to obtain long term disease control or cure. The clinical management and outcome of CML has been radically altered with the introduction of specific inhibitors of the pathogenic ABL kinase activated by the t(9;22) generating the BCR/ABL fusion protein. The cornerstone of diagnosis and monitoring, however, remains cytogenetic analysis with the addition of various molecular techniques to enhance sensitivity. In this 5th year since the introduction of imatinib mesylate, this presentation will review the laboratory investigations, both cytogenetic and molecular, that are now undertaken at all stages of the disease as well as correlating the findings to clinical outcomes in this new era of CML management. The Canadian Consensus Group on the Management of CML guidelines (CCGM-CML) will be presented and placed into perspective with emphasis on the laboratory monitoring of CML in 2006.

When is trisomy 21 not Down Syndrome? A case of transient abnormal myelopoiesis.

Rosemary Mueller, University of Alberta Hospital Cytogenetics Laboratory, Edmonton, Alberta.
Wai Etches, Divisional Director of Hematology, Department of Laboratory Medicine, University of Alberta Hospital.
Kent Stobart, Division of Hematology/Oncology. Department of Pediatrics, Stollery Children's Hospital

A baby girl, TM, was born at 34 weeks gestation to a G2P1 healthy 27 yo woman. At delivery, the baby was noted to have significant abdominal distension and hepatosplenomegaly that was confirmed by ultrasound. Baby TM was transferred to Stollery Children's Hospital in Edmonton where peripheral blood smears showed leukoerythroblastosis with 23% circulating blast cells. The main differential diagnoses were a congenital infection or a transient myeloproliferative disorder as seen in neonates with Down syndrome. Immunophenotyping results confirmed that the blast cells were of megakaryocytic origin. Peripheral blood was sent for cytogenetic analysis of unstimulated cells: 18/20 metaphases had 46, XX,+21, der(21)(q10;q10) *but* 2/20 had 46,XX with two free 21's.
Bone marrow cells: 46,XX,+21,der(21)(q10;q10)[7]/46,XX[16].
Stimulated peripheral blood: 46,XX[30]
Skin fibroblasts 46,XX[30].
Parental karyotypes from stimulated peripheral blood were normal.
Conclusion: TM was a non-Down syndrome neonate experiencing transient leukemia. Trisomy 21 was apparently limited to the leukemic population of cells. A molecular genetic model for the contribution of trisomy 21 to megakaryoblastic leukemia will be discussed.
Cytogenetic analyses were performed by Audrey O'Neil, Lynne Faist, Melanie McKay, Christine Silva and Laurel Sakaluk-Moody.

Chromosomal instability in osteosarcoma: Involvement of RECQL4 helicase.

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Osteosarcoma (OS) is an unusually aggressive sarcoma of the bone that has not been well studied by conventional cytogenetic analysis due to their highly abnormal karyotypes, which exhibit numerical and complex structural genomic alterations. Our laboratory has identified recurrent chromosomal regions (1p35-p36; 6p12-p21; 8q23-q24; 17p11-p12 and 19p13) involved in amplification and/ or rearrangement in OS. Using OS derived cell lines as a model, the genomic profile of MG63 and U2OS using array comparative genomic hybridization (aCGH) has been established. BACs probes chosen by chromosomal location using online databases were used to i) validated aCGH data and ii) define the architecture within cytobands subject to recurrent rearrangement. These results led us to the identification of a gene located at cytoband 8q23-24 that could promote genomic instability. RECQL4 gene encodes for a DNA helicase, known to have a role in stabilizing the genome. Significantly, mutations in the RECQL4 gene lead to the Rothmund-Thomson syndrome which is characterized, among other symptoms, by a higher risk of OS development. Therefore we hypothesize that haploinsufficiency of *RECQL4* could be linked to the genomic instability observed in OS in terms of either gene copy number, mRNA level or RECQL4 subcellular localization. FISH, RT-PCR and immunohistochemistry for RECQL4 were performed on 18 OS patient samples. All data will be analyzed in regard to clinical and prognosis parameters. Ultimately, our observation may lead to the establishment of a criteria suitable to classify OS samples in correlation with the prognosis.

Session II Clinical Problems
Chair, Viola Freeman, McMaster University

Two Slides Are Better Than One: Investigations report on a prenatal interphase fluorescence *in situ* hybridization (FISH) false positive result

Viola Freeman and Jack Wang, Hamilton Health Sciences

An amniocentesis was performed on a 25 yr old patient, 18 wk gestational age, with IUGR and oligohydramnios as clinical indications detected by ultrasound. Fluorescence *in situ* hybridization (FISH) was performed on the 'uncultured' amniotic fluid using AneuVysion, from Vysis. Two probe sets were hybridized side by side on one slide according to the instructions of the manufacturer. The result showed a male chromosome complement with 3 signals for chromosome 21 in 80% of the interphase scored. A normal male karyotype of 46, XY was found in our routine metaphase analysis from the *in situ* 'cultured' fluid. These discordant results generated a series of investigations.

Repeat FISH analyses were performed using the original probe set aliquot, a new AneuVysion kit with same lot number, an AML1/ETO probe, on re-made 'uncultured' and 'cultured' slides. All analyses revealed normal number of chromosome 21. The original FISH slide was re-examined and a plausible explanation for the false positive result was unveiled: one probe set was contaminated by another probe set, causing the two-coverslip junction area of the slide being hybridized by two probe sets.

Due to the seriousness of false positive results on clinical implications we have implemented the 'one probe per slide' policy as our quality control measure. This QC practice is highly recommended to all FISH consumers.

Comparison of two clinical chips

Ikuko Teshima, Hospital For Sick Children, Toronto, Ontario

Objective: To evaluate two microarrays for genome copy number of known chromosome abnormalities.
Methods: REB approval was obtained. Microarrays with loci within clinically relevant genomic regions were chosen: array with 287 clones (Vysis); constitutional array v.2 with 432 clones (Spectral Genomics). Specimens from patients with cytogenetic abnormalities were studied. This presentation will focus on a subset of these patients with microdeletions: 1p36; 4p16.3; 7q11.23; 15q11.2; 17p11.2; and 22q11.2. Reference normal DNAs were from Promega. Test and reference DNAs were labeled with Cy3-dCTP or Cy5-CTP, co-hybridized to the microarray and prepared for fluorescence detection. Forward reaction (Vysis arrays) and both forward and reverse reactions (SG arrays) were used. Arrays were scanned and analyzed: Vysis arrays - GenoSensor, Intermedico; and SG arrays – PerkinElmer ScanArray, Axon and SG SpectraWare v2.2.40. Measured signals were used to calculate the mean test/reference ratios for each target and then normalized. Thresholds for a normal range were 0.8-1.2.
Results: Both Vysis and SG arrays detected 12/12 abnormalities. Few false positives were noted.
Discussion: Features of both arrays will be described. FISH validation was not done for these cases with known abnormalities. Microarray validation of other abnormalities continue. Plans to implement use of these arrays for clinical service are underway. FISH validation, as an established method, will be required for patients found to have an imbalance by these arrays.
Conclusion: "BAC" microarrays will become part of the Cytogenetics testing repertoire.
Acknowledgements: OAML grant # SGP02-002.
V Dounaevskaia, R Lee, M Shago, G Nie, J Chen, J Ren, L Steele, P Ray, D Chitayat.
M Shackleton & D Bean (Intermedico), S Scherer TCAG & P Riley Research Institute (SpectraWare support), C Lu (PerkinElmer scanner), D Malkin (Axon software).

When normal X inactivation does not proceed as planned

Julie Kieft and James V. Higgins, Spectrum Health

A patient was referred for multiple abnormalities including microcephaly, abdominal cysts and ASD. She was found to have a karyotype of 45,X,der(X)t(X;21). The evaluation showed the loss of the X short arm from p11.2 to pter. Because of X inactivation, only the cells with the der(X) inactivated would survive. The der(X) inactivation would result in genes from the chromosome 21q being inactivated as well. We will show the karyotype and illustrate, with multiple probes, the loss of the short arm material.

The mapping and cloning of the Roberts syndrome gene (*ESCO2, RBS1*)

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Roberts syndrome is a rare autosomal recessive disorder characterized by tetraphocomelia, profound pre- and postnatal growth retardation, craniofacial abnormalities and abnormal separation of the constitutive heterochromatin regions (the RS effect). The clinical syndrome was first described by Colonel Roberts in 1919, the cytogenetic findings first described in one case by James German (1976). The RS effect was reported in four patients with diagnoses of the Roberts, SC phocomelia or pseudothalidomide syndrome by Tomkins (1978, 1979), who concluded that the over-lapping syndromes were likely due to variable expression of the same gene. In 1995, Allingham-Hawkins and Tomkins demonstrated by somatic cell complementation that the RS effect in these syndromes is caused by one gene, designated as *RBS1*. Ten years later, the gene was mapped to chromosome region 8p21.2 (McDaniel *et al*., 2005), and mutations in the gene *ESCO2* (establishment of cohesion 1 homolog 2) were found to be responsible for both Roberts syndrome and SC phocomelia (Vega *et al*., 2005). *ESCO2* is one of two homologs

coding for proteins required for proper sister-chromatid cohesion, which are targeted to different chromosome structures (Hou and Zou, 2006). This presentation will review the thirty years of research that led to the identification of the gene responsible for Roberts syndrome and recent findings in the past year regarding the role of this gene in sister-chromatid cohesion.

The impact of clinical trials on the laboratory: Strategies to deal with the rising workload due to increased number of samples and the complexity of analysis.

Kathleen Brierley, Children's Hospital of Eastern Ontario
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Many Cytogenetics laboratories are involved in clinical trials. These clinical trials not only provide valuable clinical information but can also serve to set the standard of care. They do however, lead to an increases workload in the lab necessitating the use of particular strategies to deal with their impact on workload. Algorithms can be useful tools in this regard. This talk will provide a description of the "COG" clinical trial including the requirements of the reference laboratory combined with case studies to demonstrate the efficiency and accuracy of Cytogenetics analysis and interpretation with the implementation of algorithms.

46,XX/46,XY Chimerism Detected in Opposite-Sex Twins

Rosemary Mueller, Cytogenetics Laboratory, Martin Somerville, Stacey Bleoo, Molecular Diagnostic Laboratory, Norma Jean Leonard, Medical Genetics Clinic,
University of Alberta Hospital and Department of Medical Genetics

Peripheral blood specimens from 8 yo opposite sex twins were received. The girl twin was small at 5-10% of growth curve for height and 25% for weight but otherwise normal with no features of Turner syndrome. Ultrasound examination showed a normal prepubertal uterus and ovaries. The boy twin was at the 50th centiles for height and weight and was physically normal with no abnormalities of external genitalia.
Cytogenetic analysis of peripheral blood lymphocytes gave results: 46,XY[16]/46,XX,9qh+[14]. Karyotype analysis of the male twin sibling showed 46,XY[20]/46,XX, 9qh+[10]. Analysis of microsatellite markers was undertaken by the Molecular Diagnostic Lab to determine if two sets of autosomes could be distinguished in the 46,XX/46XY cell lines. DNA microsatellite analysis of peripheral blood lymphocytes comparing 15 short tandem repeats showed double representation from both parents in 11/15 informative loci in peripheral lymphocyte DNA in each of the twins. Cytogenetic analysis of cultured fibroblasts showed 46,XX[30] in the girl twin and 46,XY[30] in the boy twin. Microsatellite analysis showed no evidence of two cell lines in these cultured fibroblasts. At this point, the evidence suggests that the chimerism in these twins may be restricted to blood cells. The scenarios of blood cell chimerism vs freemartinism vs gametic fusion to account for these results will be discussed.
Cytogenetic analyses were performed by John Duck, Christine Silva, Melanie McKay.

Double Trouble??

Silvia Trevisiol, Laura Hunnisett, Lea Velsher and Kathy Chun. North York General Hospital, Toronto, Canada.

A 37.5-year-old woman of Turkish descent and her husband were seen for genetic counseling for AMA. The couple has four healthy children and is 15 weeks into their fifth pregnancy. Due to neonatal deaths of siblings of both the patient and her husband, chromosome studies were ordered for the couple. The husband's chromosomes were normal. However, both homologues of chromosome 13 for the patient appeared identical and dicentric. Further cytogenetic stains

and FISH analyses were performed to characterize this abnormality. Meanwhile, an MSS result came back positive for Down syndrome and an amniocentesis was performed. The fetus' karyotype was normal except for having one copy of the dicentric chromosome 13. Family history revealed that the patient's parents are consanguineous. Although UPD studies for chromosome 13 were considered, due to the family history of consanguinity and no abnormal clinical features in the patient and her four children, this novel dicentric chromosome 13 is most likely a very interesting familial variant!

Efficiency and work flow in a cytogenetics laboratory

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Workload is a challenging issue for all Cytogenetics laboratories. Surveys of workload and productivity can aid in the determination of appropriate staffing levels. However, the identification of strategies to achieve optimal efficiency in a Cytogenetics Laboratory setting can be more challenging. These strategies must be designed at a local level, with much thought, careful planning, and consideration of issues that are particular to the lab in question, along with best practice standards.

Following the release of the Chromophile List Serve Survey of Cytogenetics Laboratory workloads in March 2005, the CHEO Cytogenetics Laboratory undertook an examination of current practices and considered modifications to those practices that could improve efficiency and overall work flow. The result was a vast improvement in both turn-around-time and quality.

Case reports of two patients with ring chromosome 22

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Two cases of de novo ring chromosome 22 will be described along with a brief review of the literature regarding the phenotype associated with this chromosomal abnormality. Both of the cases were referred for routine cytogenetic analysis due to developmental delay and dysmorphic features. Both patients showed large r(22) chromosomes, which contain stalks and the HIRA locus but are deleted for the ARSA locus.
Case "L" is a 3 yr old female. The pregnancy had been unremarkable. At 8 months of age she was hypotonic and not sitting. By 1.5 yrs she was sitting, and by 2 yrs she was walking with some ataxia. Her speech is significantly delayed and at age 3.5 she has no words, but is able to vocalize and gesture. She was found to have a r(22)(p13q13.3), with no mosaicism detected.
Case "B" is a 7 yr old female. The pregnancy had been notable for decreased fetal movement. She has experienced significant language delay, maintaining words by 4 years of age. She was found to be mosaic for a r(22)(p13q13.3), with 90% of metaphases having the ring and 10 % having only a single chromosome 22.

Suspect radiation exposures: Case reports from Health Canada

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Suspect cases of radiation overexposures in Canada are rare. The majority of cases that are reported come from the nuclear industry because of strict regulations that are in place to minimize doses to workers. If any exposures occur that are suspected of exceeding regulatory limits, a process is in place to analyze samples and estimate the magnitude of the exposure. Also, there

are other instances of possible overexposure, such as after medical diagnostic procedures or exposure to some radioactive source or device. Approximately three to four cases per year are submitted and reviewed by the medical officer at the Consumer and Clinical Radiation Protection Bureau, Health Canada. Cases warranting further investigation are referred on to the research team within the same department to assess the magnitude of the suspect exposure. A peripheral blood sample is collected and processed for analysis of dicentrics and rings in lymphocytes. Examination of 1000 metaphase cells can resolve exposures as low as 0.15Gy, which is a relatively high dose in terms of regulatory limits and but relatively low compared to medical procedures (equal to about 2-3 computerized tomography (CT) scans). Once the sample has been analyzed, a report describing the estimated dose exposure is generated and sent to the referring individual or institution. While the dicentric assay can provide an estimation of the total dose received, interpretation of the result is often difficult because the clinical impact of an exposure is dependent on a number of confounding variables. This presentation will give an overview of reported cases and illustrate (1) the processes involved in assessing the dose to an individual and (2) the confounding factors which impact on the clinical interpretation of the findings.

Session III: New Technologies
Chair, Elena Kolomietz, University of Toronto, Mount Sinai Hospital

Array CGH: Expanding resolution of cytogenetic analysis
Elena Kolomietz, Mount Sinai Hospital, Toronto, Ontario

Cytogenetic testing is aimed at the genome-wide analysis for the detection of chromosome aneuploidies and segmental aneusomies. Traditionally, conventional cytogenetic analysis by G-banding has performed this role and is still regarded as the gold standard. Although highly reliable for identifying aneuploidy and large chromosomal rearrangements, resolution of traditional cytogenetic techniques is limited to at best 5 Megabases (Mb), and smaller chromosomal aberrations often remain undetected.
It has recently become evident that a substantial portion of congenital abnormalities and/or MR may be caused by small genomic imbalances. The array CGH technique (Array Comparative Genome Hybridization) has been developed to detect chromosomal copy number changes on a genome-wide and high-resolution scale. Cytogenetic laboratories are now challenged to introduce and incorporate this new technique to provide optimal diagnostic services. Various applications, advantages and limitations of aCGH technology will be discussed.

Tiling path array CGH: performance characteristics for detection of DNA dosage alterations in constitutional and cancer genomes.
Doug Horsman, BC Cancer

Array-based comparative genomic hybridization (array CGH) has emerged as a powerful molecular cytogenetic tool to identify DNA dosage alterations in constitutional and cancer genomes. The BC Cancer Agency has developed an entire genome array consisting of ~27,500 partially overlapping BAC clones spotted onto a single glass slide. The array spans the human genome at an average resolution of 80 kilobases. This so-called submegabase resolution tiling path (SMRT) array was designed initially for

research purposes and, as the subject of a current Genome Canada funded project, is being evaluated as a potential clinical tool. The SMRT array can be used to investigate cancer genomes for DNA dosage alterations using fresh, frozen or paraffin-embedded tissue specimens and will detect single copy gains or losses even when the proportion of tumour cells represents only 30% of the total tissue cellularity. The array can also be used to evaluate genomic methylation changes. Performance characteristics of the SMRT array and examples of constitutional and cancer applications will be demonstrated and discussed.

High resolution oligo array comparative genomic hybridization (CGH) in the investigation of autism and neurodevelopmental disorders

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Autism is a developmental disorder of brain function that appears early in life, generally diagnosed between 18 and 30 months of age. Children with autism have problems with behavior, social interaction, imagination and communications. Autistic traits persist into adulthood, but vary in severity. While the cause is not known, many believe it to be an inherited disorder. The need to identify affected individuals as early as possible is great in order for them to receive the necessary help and services as soon as possible to minimize the damage. The financial burden on the educational system and society easily reaches the billion dollar mark.

Genomic copy number aberrations, such as chromosomal amplifications and deletions, have been associated with autistic children and their parents. Current microscopic-based diagnostic techniques such as karyotype analysis are not adequate for the resolution or the high-throughput required of a widespread test. Here we present the development of a custom 60mer oligonucleotide microarray designed for two-color CGH. This array was designed to interrogate chromosomal aberrations at high resolution associated with autism and IDIC (Isodicentric) on chromosome 15. Peripheral blood lymphocytes (PBLs) from autistic patients, immortalized with Epstein Barr Virus (EBV) were assayed for chromosomal changes at chr15 cytobands q11-13. Results show amplification of this region with well defined breakpoints and precise copy number changes unique to individual patents. Correlation of CGH to gene expression data will also be presented. By screening many patients in this manner and identifying common genetic aberrations, one can define the genes involved.

Integration of mBAND and SKY analyses of N-myc amplicons structure in neuroblastoma with high-resolution array CGH copy number profiles

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Genomic instability leads to complex patterns of chromosomal rearrangements in cancer cells. Improvements in cytogenetic banding and visualization such as M-banding and spectral karyotyping (SKY) have enabled detailed analyses on a chromosome by chromosome basis of inversions, translocations as well as the identification of regions of gains and losses in cancers of interest. Comparative genomic hybridization (CGH) measures copy number variations throughout the genome. The recent development of oligonucleotide-based array CGH technology allows detailed mapping of copy number variations including single copy changes affecting individual

genes. CGH data alone were unable to determine structural chromosomal changes like inversions and ring chromosomes and can't recognize translocation partners however can closely determine precise translocation, deletion and duplication breakpoint, and thus make karyotype analysis much more accurate. Moreover our study as well as other recent studies suggests that small focal deletions and copy number changes below the resolution of cytogenetic mapping are present at sites of some balanced translocations. Thus the combination of high-resolution cytogenetics with oligonucleotide-based CGH array provides and opportunity to study cancer genomes in unprecedented detail. In this study we tried to determine precise karyotype of 2 aneuploid tumor cell lines with N-myc amplification, retinoblastoma cell line Y79 and neuroblastoma cell line GOTO, by combination of SKY, M-band, LSI/WCP FISH and Agilent 95K genome-wide array. We present characterization of N-myc amplicons in those two cell lines and additional two neuroblastoma cell lines IMR32 and LAN5 utilizing those FISH-based cytogenetic methods and Agilent microarray.

Array CGH and FISH fine mapping of breakpoints in a patient with inverted duplication of 5p

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Objective: We report a case with inverted duplication of chromosome 5p extensively studied by array-comparative genomic hybridization and FISH.
Clinical case: A 4-year-old boy with speech and motor skill delay was studied. He initially presented as a premature newborn at 32.5 weeks with features of hypotonia, failure to thrive, seizures, and pre-auricular skin tags. Cat-like cry was not identified.
Methods: Cytogenetic analysis, fluorescence in situ hybridisation (FISH), comparative genomic hybridisation (CGH), and array based comparative genomic hybridisation (aCGH) were performed.
Results: Karyotyping revealed a *de novo* rearranged short arm of chromosome 5. FISH analysis revealed a deletion in the subtelomeric region and a duplication in the cri du chat region (5p15.31). CGH analysis showed a gain between 5p14 to 5p15.2, and a probable loss of 5p15.3-pter. Sub-megabase resolution tiling-set (SMRT) aCGH, followed by FISH with labeled BACs, demonstrated that the deletion extended from 5pter to the distal end of 5p15.31 (0-6.9 Mb), while the duplication spanned the greater part of 5p15.31 to one quarter of 5p14.3 (6.9-19.9 Mb).
Conclusions: This case is consistent with an inverted duplication with distal deletion of 5p, as demonstrated by aCGH and FISH. Correlation of genotype and phenotype in this patient, comparison with a previously reported case, and review of the mapping information from cri du chat patients allowed us to narrow down the critical region for cat-like cry to 0.6 Mb.

H. Allen Gardner Memorial Lecture:
Array CGH: moving from research to diagnostics

Arthur R. Brothman, Ph.D. FACMG, Departments of Pediatrics and Human Genetics, University of Utah, Salt Lake City, UT

The recent interest from the cytogenetics community in using array CGH (arr cgh) technology for diagnostics has been enormous. Different laboratories in both academic and commercial settings

have offered some version of this testing, primarily for the detection of constitutional imbalances. There is no current consensus, however, regarding specific aspects of implementing arr cgh into the general health care system. Protocols for validation, confirmation, source of control DNAs, data interpretation and identification/reporting of copy number variants need to be considered. Reimbursement issues including source of the chip used and whether confirmatory studies should be billed also must be addressed. At the University of Utah, we initially began using arr cgh to characterize prostate and other tumors, and not only confirmed previously identified abnormalities, but greatly increased the amount of information obtained from small tumor samples. We have implemented an algorithm for offering arr cgh clinically, using the two BAC array platforms available through Spectral Genomics, Inc. (recently acquired by Perkin Elmer). Examples of research and clinical analyses will be discussed, as will our approach to dealing with some of the issues involved in using this new technology for diagnostics. Upcoming Standards and Guidelines through the American College of Medical Genetics, the inclusion of “arr cgh” nomenclature in the ISCN 2005, and the general acceptance of this valuable technique by the cytogenetics community are all indicators that this will develop into a significant aspect of our testing repertoire in the future.