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ABSTRACTS

Late posters

608: Antioxidants, folate and MTHFR polymorphism studies in acute lymphoblastic leukemia (ALL)

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Acute leukemia (AL) is the most common cancer in children representing about one half of all cancers among persons younger than 15 years. Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) each represent a heterogeneous complex of disorders, which result from diverse mechanisms of leukemogenesis. In ALL, research is being increasingly placed on the elucidation of the etiological factors and mechanisms involved in the disease development. Since Leukemia's are malignancies arising from rapidly proliferating clones of haemotopoietic cells, thus having greatest requirements for DNA synthesis, attention has recently been focused on the genes or environmental factors that can play a role in an individual's susceptibility to DNA damage. Oxidants play a role in several stages of carcinogenesis. Production of reactive oxygen species (ROS) is an inevitable result in cells that use aerobic metabolism for energy production. ROS can be important mediators of damage to biomolecules such as DNA, proteins, and lipids, leading to cellular dysfunction and cell death. Accumulation of such molecules causes noxious effects on individuals, resulting in diseases such as hematopoietic malignancies. Folate, a key element in the one-carbon group metabolism, is essential for normal mammalian cell growth. The folate metabolic pathway is crucial in purine and pyrimidine synthesis, as well as in the provision of methyl groups for DNA, RNA and protein methylation. Disruption of homeostasis in the one-carbon pool, has been shown to affect the risk of several cancers. Alterations in this metabolic pathway can occur due to genetic variation at any of the enzymes directly involved in maintaining homeostasis of the one carbon pool. Methylenetetrahydrofolate reductase (MTHFR) is a central enzyme in the metabolism of folate and methionine, both important factors inmethylation and DNA synthesis in humans. The enzyme catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, and it has been shown that the reduction in its activity resulting from polymorphism in the MTHFR gene can modify the susceptibility to cancer. Our studies focused on the antioxidant, immunophenotyping and MTHFR polymorphism in acute lymphoblastic leukemia (ALL) children. From our results it shows the antioxidant levels were significantly reduced, folate levels and MTHFR polymorphism shows the protection against ALL.

609: Relationship between down-regulated expression of motility-related protein-1 (MRP-1/CD9) and characteristics of gastric cancer

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Objective: To explore and identify genes related to gastric cancer and its premalignant lesions, and to analyze expression profiles of the differentially expressed genes.
Methods: The differentially expressed cDNA bands were assayed by fluorescent mRNA differential display (FDD) from gastric cancer specimens, matched with normal gastric mucosa and premalignant lesions. The mRNA expression of motility-related protein-1 (MRP-1/CD9) gene was studied by RT-PCR and Northern blotting in different kind of gastric tissue. The protein expression of MRP-1/CD9 was assayed by Western blotting.
Results: In contrast, a differentially expressed cDNA fragment named G1, exhibited lower expression in all gastric cancers compared to the matched normal gastric mucosa and premalignant lesions. A BLASTN search for sequence homology performed in the GenBank revealed that the sequence of G1 was identical (100% homology) to that of the 3′ end of human MRP-1/CD9 mRNA. Northern blotting analysis confirmed the differential expression of MRP-1/CD9. RT-PCR analysis showed that the MRP-1/CD9 gene was expressed at much lower rate in gastric cancer (0.31 ± 0.18) compared to the matched normal gastric tissue (0.49 ± 0.24) ($P = 0.001$) and premalignant lesions (0.47 ± 0.18) ($P = 0.041$). Furthermore, MRP-1/CD9 mRNA expression in diffuse-type of gastric cancer (0.22 ± 0.17) was much lower than that expressed in intestinal-type of gastric cancer (0.38 ± 0.16) ($P = 0.015$). Western blotting analysis showed that the MRP-1/CD9 protein was expressed at much lower rate in gastric cancers (0.21 ± 0.13) compared to the matched normal gastric tissue (0.46 ± 0.19) ($P = 0.001$) and premalignant lesions (0.42 ± 0.14)

($P = 0.001$). MRP-1/CD9 protein expression in diffuse-type of gastric cancer (0.20 ± 0.11) was much lower than that expressed in intestinal-type of gastric cancer (0.39 ± 0.12) ($P = 0.002$).
Conclusion: The MRP-1/CD9 expression was down-regulated in gastric cancer and its expression may be related to the carcinogenic process and histological type of gastric cancer.

610: Amyotrophic lateral sclerosis: a promising therapeutic approach, from laboratory to clinical implications

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Amyotrophic lateral sclerosis (ALS) is a late-onset progressive degeneration of motor neurons occurring both as a sporadic and a familial disease. The etiology of ALS remains unknown, but one fifth of instances are due to specific gene defects, the best characterized of which point mutations in the gene is coding for Cu/Zn superoxide dismutase (SOD1). Because sporadic and familial ALS affects the same neurons with similar pathology, it is hoped that understanding these gene defects will help in devising therapies effective in both forms. A wealth of evidence has been collected in rodents made transgenic for mutant SOD1, which represent the best available model for familial ALS. Mutant SOD1 likely induces selective vulnerability of motor neurons through a combination of several mechanisms, including protein misfolding, mitochondrial dysfunction, oxidative damage, cytoskeletal abnormalities and defective axonal transport, excitotoxicity, inadequate growth factor signaling, and inflammation. Damage within motor neurons is enhanced by noxious signals originating from nonneuronal neighboring cells, where mutant SOD1 induces an inflammatory response that accelerates disease progression. We observed that lipid peroxidation in the erythrocytes of amyotrophic lateral sclerosis patients significantly increased with respect to controls. On the other hand, catalase activity was found to be significantly lower. The activities of glucose-6-phosphate dehydrogenase, glutathione reductase and glutathione levels were also found to be significantly reduced in ALS patients compared to healthy subjects. It was further observed that lipid peroxidation started to increase and catalase, glutathione reductase, glucose-6-phosphate dehydrogenase enzyme activities and glutathione levels started to decrease as amyotrophic lateral sclerosis progressed from 6 to 24 months, suggesting a correlation between these parameters and duration of amyotrophic lateral sclerosis. This study confirms the involvement of oxidative stress during the progression of amyotrophic lateral sclerosis and the need to develop specific peripheral biomarkers. The clinical implications of these findings may lead to promising therapeutic approaches.

611: Drug target prioritisation from metabolic pathways

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The process of drug discovery for pathogenic infections has undergone a paradigm shift in the last two decades. Target identification and lead discovery/optimisation are two of the main components of the drug discovery cycle where computational strategies have had maximum impact. Rational methods for drug design have replaced screening and serendipity, shifting the process of discovery to identification of novel drug targets from pathogenic organisms. The development of a pipeline which can link drug discovery from drug target identification to inhibitor design is desirable especially in the post-genomic era where complete genome sequencing projects have greatly facilitated the process of unraveling the full repertoire of biological functions that an organism possesses. For a pathogenic organism, such a compilation of functions has a direct implication in discovering potential drug targets, for example, identifying virulence factors, searching for membrane transporters or uncharacterised genes which are conserved across a large number of genomes, selecting genes or functions which are unique to the pathogen and not present in the host organism etc. We have applied a method developed in-house, which uses function specific Hidden Markov models for accurate identification of metabolic enzymes from genome sequences. This protocol, ModEnzA, incorporates sequence clustering and enrichment of the training sequences. We compare our method with other enzyme identification methods, namely PRIAM, MetaShark and EFICAz for genome-wide enzyme identification in *E. coli*, *B. aphidicola*, *M. pneumoniae* and *P. falciparum* genomes. ModEnzA outperforms the other methods in terms of specificity and sensitivity. The ModEnzA protocol is applied for enzyme identification from 664 bacterial genomes. Potential drug targets are prioritized from the list of metabolic enzymes using graph-theoretic representations of metabolic networks. We prioritise drug targets in terms of chokepoints (those enzymes which either produce and/or consume a unique metabolite), breakpoints (enzymes whose removal from the metabolic network results in an increase in the number of strongly connected components) and the presence/absence of alternate pathways that can circumvent a deleted enzyme in the metabolic network. We apply this protocol for generating lists of potential drug targets from the pathogens *M. tuberculosis* and *P. falciparum.*

612: SimOrg—a novel computational software for system variable analysis

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Aim: The aim of this project was to develop an indigenous and original software program which could be used to model various systems e.g. life processes of organisms using a mathematical approach—an algorithm which could be input by the end-user and the software would show the changing values in the form of a graphical representation. The various parameters can give a detailed 'analytical' overview concerning the life processes of the organisms and their related variables. Analysis of variables in a system is always a fundamental problem for many bioinformatics case-studies and other procedures. If a basic model of system's variables can be determined empirically or theoretically, then one invariably needs a simulation platform on which to run the algorithm. SimOrg is a novel software which achieves this, and much more.
The main idea: When in a certain area (Array), a particular Organism/System/Unit exists in a particular region (Cell), its survival may depend on certain factors such as Locomotion, Reproduction, Intelligence etc. These factors usually depend circularly on each other e.g. more Intelligence may mean more levels of Locomotion; which in turn may imply a bit lower Reproduction efficiency. This behavior of Organisms or a Unit can be roughly simulated through mathematical expressions, if they have been already established or found out. It should be noted that the variable types mentioned here like Locomotion, Reproduction etc. are just for representative purposes only and for the correct running of the program with default values. The end-user may propose any other model with different variables too; so

that an entirely new system may be simulated. In addition to this, these Organisms/Units may also get affected by the external changes in the environment. These external factors may change randomly and may not get significantly affected by the Organisms. But they do have their affects on the Organisms' life parameters.
Coding environment: The software was made and compiled for final distribution as an exe file using the registered copy of developing environment of Game Maker 6.0, a freeware utility for making Games and other Software.

613: Integration of genomic expression data into the etiopathogenetic clusters—important step in teaching/learning of medicine

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The exponential growth of information, nonlinear behavior of pathobiological system and increasing complexities of conceptual models have imposed the unique demands on educational system and methodology in medicine. Comprehensive enrichment of classical human pathophysiology with the genomic data is still pending issue. Powerful computing systems, sophisticated morphological methods and postgenomic throughput quantities of molecular data are providing new insights into the processes underlying clinical presentations. On the other side, students and practicing doctors are inclined to limit their scope to the given branch within the system of compartmentalized medicine. Educational curricula are often designed according to the similar pattern. Evidence based medicine may be considered as the attempt to bridge the chasm of contemporary medicine. Pathophysiological interpretations of natural history of diseases and disorders aim to integrate vertical dimension (from the molecule to symptom), horizontal dimension (simultaneous involvement of multiple systems), as well as longitudinal dimension (natural course) of the problem. In order to achieve such integration, we have been using a matrix-designed, problem-solving educational model. This model contains four steps. Exposition of problem (1), repetition of knowledge (2), algorhythmic workout (3), and feedback integration of the problem (4) reiterate and put together the heterogeneous facets of the same issue. The etiopathogenetic pathways are outlined as dominant, contextual, parallel, and sequential, as well as the branching points. This four-step approach clearly depicts etiopathogenetic pathways and networks of interconnected elements within the hierarchy of the system. Some nodes within the networks (e.g., disturbed gene expression, structural alterations, concentration abnormalities, etc.) form the clusters, with multiple entries and outputs. Focusing to such clustering points may become a reliable approach to master complexities in medicine. Relevant genomic data are molecular pillars of such clusters. Both qualitative and quantitative aspects of gene expression are adding up to classical interpretations. Since this model is the opened matrix, new data can be easily incorporated at the appropriate place. They are corroboration and/or challenging information within the context of networks of hierarchical system. Basic etiopathogenetic pathways and clusters are enforced and solidified into reliable framework of pathobiological processes.

614: Tricentric Y chromosome mosaicism in a Turner syndrome—clinical cytogenetic and molecular studies: a new case report

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We report here a new case of Turner syndrome with a "tricentric Y chromosome" mosaicism. The proband, a 21 year-old female with h/o primary amenorrhoea and very few clinical features of typical Turner syndrome, was investigated to rule out Turner syndrome. Routine chromosome analysis from peripheral blood culture using G-banding technique showed mos 45,X/46,X,der(Y) [75;25]. A few cells with iso(Yp) [4%] and 47,X,der(Y), + ring(Y) [1] were also observed. FISH analysis using Centromeric probes for X and Y chromosome, WCP Y (heterochromatin) and SRY confirmed one X chromosome and the derivative Y chromo with three centromeres (CEP Y +++) and two copies of SRY. PCR analysis of the genomic DNA confirmed positive for SRY (Yp11.3), ZFX/Y (Yp11.3/Xp22.3-p21.3), AZFa (Yq11.21), AZFb((Yq11.22) and AZFc(Yq11.23). Karyotype of the mother is normal 46,XX. Father and an elder brother of the proband were not available for investigation. Histopathology of bilateral streak gonads (both left and right) showed atrophic tubules containing only sertoli cells (Testicular tissue). No gonadoblastoma was observed. She is responding well to HRT therapy. Despite the presence of a Y chromosome and SRY gene (two copies), she did not show any signs of virilization except for a reduced growth rate (Ht. 154 cm at 21 years). Mosaicim for dicentric Y chromosome, iso Yp or iso Yq or known in Turner syndrome cases with a derivative Y chromosome. However, tricentric Y chromosome has not been reported in the literature. This is the first report of a TRICENTRIC Y chromosome to the best of our knowledge. There are only four cases of tricentric chromosome reported in the literature (Chromosomes 9, 15, Acrocentric chromosomes and X—Borgaonkar DS, chromosomal variation in man—online database, Wiley, 2008). The clinical significance the mosaicsm and origin of the tricentric Y chromosome will be presented.

615: Risk assessment of drug-like molecules by in-silico quantitative structure toxicity relationships

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In the early stage of drug discovery, especially for computer-aided design, a large number of molecules will be proposed as potential leads and that the bioactivity risk of these molecules is expected to be evaluated prior to synthesis. The rule-based expert systems have been used for the aim, while mining of a large amount of toxicological data can provide us with another promise.

In the present study, an initial analysis to a toxicological database of chemicals is made. Then a stepwise strategy is provided to chemical data mining of toxic chemicals, which combine principles of QSAR study with structure-activity clustering. QSTR (Quantitative Structure Toxicity Relationship) predictive models were developed using QSAR method with database of 612 compounds provided by Environment Protection Agency (EPA). These models, which are developed, allow prediction of acute toxicity (LC50) of chemical compounds generally used for risk assessment of drugs prescribed and environmental disaster management. The QSTR methods are fast, economic and powerful screening tools, and also contribute to the reduction of the animal use in biological activity studies. These models were successfully tested by applying on the cancer database,

which contained molecules elucidated on the basis of scaffold-based approach. This helped to evaluate the extent of toxicity of active molecules in the cancer database. Thus this approach promises a good risk assessment model to predict toxicity for any dataset containing active drug molecules.

616: Association of ADH1B and ALDH2 gene polymorphisms with alcohol dependence: a pilot study

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Background: Functional polymorphism in ADH1B and ALDH2 genes are considered most important among several genetic determinants of alcohol dependence (AD), a complex disorder.
Aims: There is no report on the widely studied Arg47His and Glu487Lys polymorphisms from Indian alcohol dependent population. We, for the first time, report allelic and genotypic frequencies of Arg47His and Glu487Lys SNPs in North Indian alcohol dependent subjects.
Methods: A total of $n = 174$ alcohol dependent males, recruited using DSM IV criteria, were genotyped using PCR–RFLP method.
Results: Data obtained from genetic analysis was correlated with clinical parameters using *T* test or Mann Whitney's U test. ADH1B gene polymorphism was found to be largely monomorphic with minor allele frequency (ADH1B-2) less than 0.001. For the ALDH2 Glu487Lys SNP, genotypic frequencies were 0.73 (2-1/1), 0.16 (2-1/2) and 0.11 (2-2/2), with minor allele frequency (ALDH2-2) = 0.19. Various clinical parameters were found to be significantly associated with ALDH2 polymorphism.
Conclusions: The highlight of the study is a clear association of ALDH2 gene polymorphism with delayed onset and shorter duration of alcohol consumption among ALDH2-2/2 individuals. Our finding bolsters the protection conferring property of the ALDH2-2 allele of Glu487Lys SNP of ALDH2 gene.

617: Synergistic interplay between *Helicobacter pylori* virulence genes and host COX-2 and iNOS enhances the risk of gastric cancer

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Background and Aim: *H. pylori* (Hp) strains vary in their carcinogenic potential. Both host factors and bacterial factors have been postulated to contribute to the variable outcome. Over expression of host COX-2 (encoded by the PTGS2 gene) and iNOS (encoded by the NOS2A gene) has been implicated in the development of gastric carcinoma. Furthermore, the link between genotypes in relation to COX-2 and iNOS expression and disease status needs to be determined. Therefore the present study addressed to identify Hp-bearing hosts who are at greatest risk of developing precancerous lesions.
Methods: A total of 240 subjects with various gastric disorders were screened. Genotyping based on cagA, cagE, cagT, vacA signal region and hrgA genes of Hp was performed using DNA from gastric biopsies. Expression of COX-2 and iNOS was assessed by RT-PCR and immunoblotting. Histological scoring of antral and corpus biopsies for the presence precancerous lesions was done.
Results: Genotype cagA+/cagE+/cagT+/hrgA+/vacAs1 showed high prevalence 73.7%. Among which 81.1% had overt gastric disorders whereas 46% subjects had less severe gastric disease. Histology revealed presence of atrophy in 52 vs. 18%, IM in 32 vs. 9% and dysplasia in 20 vs. 4% respectively (Statistically significant at *p*-0.01. RT-PCR and immunoblotting data showed high expression patterns of COX-2 and iNOS in overt gastric disorders than with less severe gastrointestinal disorders.
Conclusion: Genotype cagT+ve/hrgA+ve/cagA+ve/cagE+ve/vacAs1 +ve and heightened expression levels of COX-2 and iNOS have higher differentiating and predictive value for the development of severe disease manifestations. This suggests that Hp induced gastric inflammatory reaction to be influenced by multiple factors, and probably results from the synergistic effect of bacterial virulence and host factors, which work together in a complex way causing various diseases in the host.

618: Structure based drug designing for HIV-1 reverse transcriptase protein

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Nevirapine and its structural derivatives are important non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs). Nevirapine may cause severe or life-threatening liver toxicity, usually emerging in the first 6 weeks of treatment. The most common adverse effect of nevirapine is the development of mild or moderate rash. Severe or life-threatening skin reactions have been observed in patients, including Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity. Therefore there is a need and urge to develop a new drug having minimum adverse effects and high effectiveness. In this work, nine nevirapine analogues were studied. ChemSketch software was used to design/draw new structural derivatives. VEGAZZ software was used to dock nevirapine into its target (HIV-1 RT) and binding energy in the form of energy score was developed. Out of nine derivatives, substitution of H with CH3 at the different positions, as well as substitution of O with S at the B position in analogues, were found to be the most potent in comparison with the template nevirapine (which is used currently as the drug candidate). All the analogues also passed the absorption, distribution, metabolism and excretion (ADME) screening and Lipinski's rule of 5, and have the potential to be used for second-generation drug development. The work demonstrates that ChemSketch-VEGAZZ and ADME screening (ADMETox) is a promising approach to predict the binding activity of ligands to the receptor and further screen for a successful candidate drug in a computer-aided rational drug design.