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TRACK 5(I)

PHARMACOGENOMICS

TRACK 5(II)

POSTGENOMICS: DRUG AND BIOMARKER DEVELOPMENT

02 November 2010 (Tuesday)

SESSION CHAIR : **DR. MICHAEL J. SHAPIRO**
University of Maryland School of Pharmacy, Baltimore, USA

SESSION CO-CHAIR: DR. MICHAEL FIRER
Ariel Center for Applied Cancer Research, Ariel University Center, Israel

SESSION INTRODUCTION

TITLE: INTERSECTION OF BIOPHYSICAL STUDIES AND DRUG DESIGN. USE OF THE "EFFICIENCY COEFFICIENT" AND "DRUG DESIGN MATRIX."

DR. MICHAEL J. SHAPIRO, University of Maryland School of Pharmacy, Baltimore, USA

TITLE: M-PROTEIN BINDING PEPTIDES FROM PHAGE DISPLAY LIBRARIES AS BIOMARKERS IN MULTIPLE MYELOMA: A PARADIGM FOR EARLY DETECTION OF DISEASE RELAPSE

DR. MICHAEL FIRER, Ariel Center for Applied Cancer Research, Ariel University Center, Israel

TITLE: MULTIPLE RECEPTOR DOCKING AND DOCK POSE CLUSTERING AS A TOOL FOR COMFA AND COMSIA STUDIES

DR. M. VIJJULATHA, Department of Chemistry, Nizam College, Hyderabad, India

COFFEE BREAK & POSTER SESSION

TITLE: PHARMACOGENETICS /PHARMACOGENOMICS: AN OVERVIEW

DR. SACHDEV YADAV, Department of Pharmacy, Department of Biosciences and Biotechnology Banasthali, India

TITLE: LEAD MOLECULES FOR MOLECULAR MEDICINE AND OMIC STUDIES

DR. S V ESWARAN, St. Stephen's College , University of Delhi, India

TITLE: QSAR AND DRUG DESIGNING FOR ANTI-TUMOR/ANTI-CANCER ACTIVITY

DR. RAMA PANDE, School of Studies in Chemistry, Pt. Ravishankar Shukla University, India

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Intersection of Biophysical Studies and Drug Design. Use of the "Efficiency Coefficient" and "Drug Design Matrix"

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As we all know, the NCE that reach market have been dwindling even though our ability to use technology has increased. This might be due to the fact that all the easy targets are well studied and only the intractable systems are being investigated and/or; this means we must be doing something fundamentally incorrect. In the seminar today, I will present the basis of fragment based drug design and some of the tools that can be used to evaluate what to do next. In addition I will discuss the limitations of some of tools in understanding molecular recognition and perhaps what we can do about this situation. I will also talk about some of our results using NMR spectroscopy, which unfortunately has fallen out of favor recently in the drug discovery process, showing how it can aid the understanding of the molecular recognition process by providing us information not easily attainable by any other method.

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M-protein Binding Peptides from Phage Display Libraries as Biomarkers in Multiple Myeloma: a Paradigm for Early Detection of Disease Relapse

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The detection of specific biomarkers with simple laboratory tests can may important implications in the diagnosis, treatment and survival of patients. An example is Multiple Myeloma (MM), an incurable B-cell leukemia. With the use of new drugs, most MM patients now enter into a period of remission; however they inevitably relapse. MM tumor cells derive from a single clone of plasma cells that usually express and secrete excess amounts of clonotypic immunoglobulin (M-protein). Within each patient, M-protein V_H gene sequences differ suggesting that these antibodies are directed against different antigens. Currently, electrophoresis and gel immunofixation are used to identify the presence and isotype of M-proteins in serum, however these methods are both tedious and insensitive. Particularly with regards to early intervention in patients in remission, a more sensitive method that heralds the presence of the specific M-protein biomarker would indicate disease relapse, leading to earlier resumption of treatment and potentially enhanced patient survival. To this end, we have used phage display peptide libraries to isolate peptides that bind M-proteins from MM patients. Bioinformatic analyses of the peptide sequences determined their homology to natural proteins of clinical significance including proteins from bacterial species associated with respiratory infections and food poisoning. These peptides can then be conjugated to fluorescent or other reporter molecules and used in simple immunoassays to follow the reappearance of the patient's M-protein in serum. The isolation of biomarker-binding peptides and their use in sensitive immunoassays is a platform approach that can be applied to development of improved methods for the monitoring of patients.

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Multiple Receptor Docking and Dock Pose Clustering as a Tool for CoMFA and CoMSIA Studies

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This study was performed on 13 high resolution receptor conformations of HIV-1 protease extracted from protein data bank (1PRO, 1BVG, 1BV9, 1AJX, 1AJV, 1T7K, 1QBR, 1QBS, 1QBU, 1HVR, 1HVH, 1DMP, 1G35). A set of 150 cyclic urea protease inhibitors with diverse substructures and varied range of inhibition constants, were docked into the active site of the receptors. After analysis their binding affinities and interactions with the receptor, the docked poses were clustered to obtain the best receptor binding conformation. These dock poses from clustering were used for 3D QSAR analysis, statistically significant CoMFA and CoMSIA models were generated using 85 molecules in the training set by applying leave one out cross validation study r^2_{cv} values of 0.663 and 0.623 for CoMFA and CoMSIA respectively and non-cross validated values of 0.985 and 0.959 were obtained for CoMFA and CoMSIA respectively. The predictive ability of these models was determined using a test set of 65 cyclic urease molecules that gave predictive correlation (r^2_{pred}) of 0.54 and 0.67 respectively for CoMFA and CoMSIA indicating good internal predictive ability. Based on this information 25 non-cyclic urease molecules were taken as a test set to check the external predictive ability of these models. This gave remarkable out come with r^2_{pred} of 0.68 and 0.51 for CoMFA and CoMSIA respectively. This approach is applicable for receptor based alignment for molecules having varied structural motifs, recommending the increase in accuracy of 3D QSAR predications for considering diverse scaffolds.

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Pharmacogenetics / Pharmacogenomics: An Overview

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Interindividual differences in response to drug: Pharmacogenetics / Pharmacogenomics. Vogel in 1959 first proposed the term "*Pharmacogenetics*. Over 50 years down the lane examples of exaggerated responses to drugs, novel drug effects, or lack of effectiveness of drugs as a manifestation of inherited individual traits have been observed. Genetic factors influence a drug's action by affecting pharmacokinetic and pharmacodynamic properties. Unexpected, uncommon, or "abnormal" effects of drugs may be associated with certain genetically transmitted disorders. Under these circumstances, the modified drug response may have both diagnostic and therapeutic implications. These interindividual differences in response to drug are determined by combination of different factors; Physiological factors (sex, age),Pathological factors (liver disease, renal disease), Environmental factors (other drugs, diet, smoking),Genetic factors.How important each of these factors is, varies from drug to drug and individual to individual. So, pharmacogenetics explores the genetically determined alterations in the drugs usual metabolic pathways and these alterations are associated with the accumulations and toxicity of a drug and shifts to different pathways that have toxic intermediates. The extent to which genetic factor determine drug responsiveness is investigated by the means of population, family and twin studies. Goal of Pharmacogenetics;to understand how someone's genetic make up determines how well a medicine works in body, what side effects are likely to occur, thus making it a field of growing interest in medicine and pharmaceutical industry? The method of "genomics" have been increasingly applied to pharmacogenetics research as it emphasis on molecular structure and functions of genes. A relatively recent addition to the discipline is the field of "ecogenetics", which concerned with dynamic interaction between an individual genotype and environmental agents.Benefits; Pharmacogenetics studies have a vital role to play in every step involved in;Drug Discovery; Pathway Identification,Target Identification, Selection, Screening, Characterization, Validations.Drug Development; Preclinical studies, Clinical studies, Safety of the product launched in a population can be predicted with the availability of pharmacogenetic profile of drug, Marketing aspect of the drug.

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Lead Molecules for Molecular Medicine and Omic Studies

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In this paper, new compounds synthesised during the last three and a half decades will be presented. These molecules have become intertwined with omic studies and could serve as leads for molecular medicine. Six such compound classes will be discussed here.

- Methoxyisoxazole quinones prepared have been shown to be potent radiosensitisers *in vitro* for human cancer / tumour cells, which had stopped taking up further radiation.
- New nitrophenyl azides prepared have been shown to exhibit inhibitory activity against *Crotalaria juncea* (Jute) and *E. coli.* In the former, these showed '2, 4-D' like activity. The corresponding amines were used to synthesise biologically interesting 9-Aryl-9H-Purine-6-amines. This work has been cited in a recent patent.
- 5, 6- Dimethoxybenzofuroxan, which exists in two rapidly equilibrating degenerate forms has been shown to possess antifungal activity against *Candida albicans* and other fungi. Based on this benzofuroxan, a new indoloquinoxaline dioxide has been synthesised which could show antibacterial activity.
- A short synthesis of Pyrroloquinoline quinone, P. Q. Q. (Methoxatin) has been developed. This compound is considered to be a new vitamin to prevent heart attacks and strokes.
- New homo and hetero bifunctional crosslinkers have been developed. Similar reagents could be designed based on P.Q.Q., which will be employed for proteomics. Cholesterol /steroid photolabels are also being prepared for lipidomics.
- Dehydrodivanillin, a natural product has been used to prepare antifungal 1, 2, 3-triazoles using the Click reaction.

In vivo and *in vitro* studies are being undertaken for all the above compounds to unravel the underlying biological mechanisms. This has a great potential in the area of omic studies and for developing better diagnostic tools for molecular medicine.

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QSAR and Drug Designing for Anti-Tumor/Anti-Cancer Activity

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QSAR is the science which relates chemical structure of biological activity. N-arylphydroxamic acids of general formula, $R_1NOH.R_2C=0$, where R_1 and R_2 are phenyl or/and substituted phenyl groups are biomolecules as (i) They follow the "Lipinski Rule of 5", (ii) Contain both HBD and HBA sites. These molecules are neutral polyfuncitonal molecules and hydrogen-bonds helps in drug delivery system by providing binding interaction with receptors. The hydrophobic, electronic and steric parameters of 20 such molecules are derived following the experimental techniques along with computation methods. The antiproliferative effect of these molecules was studies in-vitro and and in-vivo. The biological parameters like concentration, time intervals and survival period are also measured. Based on these data the mechanism of death of cancerous cell is studied under the heads, (i) ROS, (ii) Mitochondrial potential (iii) Lipid peroxidation and (iv)DNA Ladder. The QSAR parameters determined are correlated with biological activity estimated, following the MRA and PLS methods and the potency of molecules are computed, by formulating and generating the equations for the molecules under study. All the molecules investigated show anti-tumor activity when tested in-vitro. One molecule, N-p-Chlorophenys-4-bromobenzohydroxamic acid with best IC_{50} value (53 micro molar) is selected for in-vivo experiments. The results show that 100 mg of this molecule kills 90% cancerous cells in 16 days, per kg. wt. of mice with the clean death of cancerous cells.

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Pharmacogenetic Study of Apo A5, Cetp and Mthfr Polymorphisms on Fenofibrate Therapy in Tunisians Type 2 Diabetic Patients

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Fibrates act to attenuate atherogenic dyslipidemia in type 2 diabetic patients. However an increase of serum homocysteine (tHcy) after fenofibrate treatment has been reported, compromising its cardiovascular benefit. Polymorphisms in candidate genes related to lipid, lipoprotein and tHcy metabolisms were suspected to influence this response. The association between polymorphisms in cholesteryl ester transfer protein (CETP), apolipoprotein A5 (apo A 5), and methylenetetrahydrofolate reductase (MTHFR) genes in response to fenofibrate treatment ((200 M) for 4 weeks was evaluated in twenty one type 2 diabetic patients.

After fenofibrate use a significant decrease of TG level (29%) and a decrease of total cholesterol ($p = 0.081$) and CETP activity ($p = 0.089$) were noted. However, the HDL-C concentration has increased ($p= 0.081$) while LDL-C levels did not vary. Moreover, the prevalence of hyperhomocysteinemia, rose to 100%.

Both apo A5 TT and TC carriers showed significant decrease of TG levels. Whereas the HDL-C variation is better in TT genotype (23.5% vs -1.3% for TT and TC respectively; $p = 0.062$). The decrease of TG levels after fenofibrate treatment is more important in B1B1 than in B2B2 genotype of CETP polymorphism. Only B1B1 homozygous showed a decrease of CETP activity and an increase of HDL-C. After fenofibrate use, the increase of tHcy levels was more important in MTHFR T carriers than in CC homozygous (39.97 ± 14.77 vs. 28.02 ± 8.59 µmol/l, respectively).

Pharmacogenomic studies have a great economic and health interest for a better treatment of type 2 diabetic patients.