PEMED 2018

Personalized and Precision Medicine

International Conference

June 25-27, 2018 | Paris

BOOK OF ABSTRACTS

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Polypharmacology of Anti-Cancer Antibodies

Monday, 25th June - 09:05 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 96

Prof. Yosef Yarden [1]

1. *Weizmann Institute of Science*

Both biological and pathological networks acquire robustness due to their modular structures. Hence, effective pharmacological interception of oncogenic networks requires polypharmacology, namely the use of pharmaceutical agents acting on multiple targets or disease pathways. Along with the ability of drug combinations to block acquired resistance to targeted cancer therapies, polypharmacology often translates to enhanced toxicity or adverse effects. Kinase inhibitors that simultaneously blocks several protein kinases exemplify the potential of polypharmacology. Thus, sorafenib, a drug approved for treatment renal cell cancer and hepatocellular carcinoma, inhibits two receptors, VEGFR and PDGF-receptors, as well as three members of the Raf family of cytoplasmic kinases.

In general, monoclonal antibodies (mAbs) elicit milder side effects, hence their use in combinations holds promise. However, due to the mono-specific nature of mAbs, their use in polypharmacology requires either applications of antibody mixtures or the use of genetic engineering (to design bi- or tri-specific antibodies). Remarkably, the immune system makes extensive use of polyclonal, rather than monoclonal antibodies. My lecture will describe pioneering, relatively effective and safe mixtures of mAbs, both approved and experimental. Lessons learned with treated breast cancer, melanoma and lung cancer will be discussed in an effort to define the principles governing effective utilization of antibody polypharmacology in oncology.

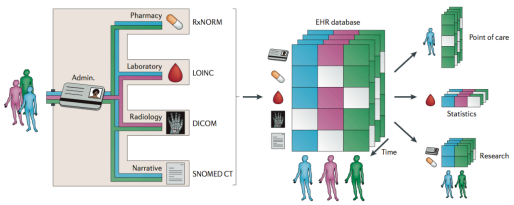
Population-wide data and text mining of electronic health records

Monday, 25th June - 09:40 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 186

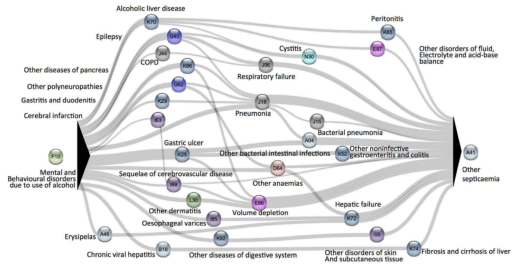
Prof. Lars Juhl Jensen [1]

1. *University of Copenhagen*

Clinical data describing the phenotypes and treatment of patients is an underused data source that has much greater research potential than is currently realized. Mining of electronic health records has the potential for revealing unknown disease correlations, for better stratifying patients, and for improving post-approval monitoring of drugs for adverse drug reactions. In my presentation I will introduce the centralized Danish health registries and show how we use them for identification of temporal disease correlations, discovery of common diagnosis trajectories of patients, and thereby stratification of patients. I will also describe how we use text mining extract information also from the clinical narrative in electronic health records and use this for identification of new adverse reactions of drugs.



Electronic health record content.png



Alcohol-related sepsis trajectory network.png

DIAGENODE: Epigenomics Profiling Services

Monday, 25th June - 10:15 - Exhibitor Short Talk - Amphitheater - Plenary Speech - Abstract ID: 189

Dr. Matteo Tosolini [1]

1. *Diagenode*

Diagenode is a leading global provider of complete solutions for epigenetics research, biological sample preparation, and diagnostics assays based in Liege (Belgium), USA, Japan and Chile. The company has developed a comprehensive approach to gain new insights into epigenetics studies. Diagenode offers innovative Bioruptor® shearing device and IP-Star® automation instrument, reagent kits, and high quality antibodies to streamline DNA methylation and ChIP-seq workflows. Furthermore we provide a wide range of end-to-end epigenomics profiling assays. To study chromatin, we offer ChIP-seq (Chromatin immunoprecipitation) in order to identify histone modification distribution and transcription factor binding-sites at a genome-wide level. In addition, we provide as well ATAC-seq (Assay for Transposase-Accessible Chromatin) to map chromatin accessibility genome-wide. To analyze DNA methylation, we offer WGBS (whole genome bisulfite sequencing), RRBS (reduced representation bisulfite sequencing) which focuses on CpGrich regions and pyrosequencing which allows for targeting specific regions of interest. Regarding RNA we propose transcriptome analysis for miRNA and small RNA, messenger RNA (poly A-selected) and total RNA with lncRNA (rRNA depleted). A dedicated project manager will help you design your project and reports on a regular basis on its progress. Once samples have been sequenced we perform cutting-edge bioinformatics analysis and produce high quality publication-ready data. With more than 15 years of expertise in Epigenetics Diagenode is the ideal partner for your research project.

Pharmacogenomics and Epigenetics: Update and Future Directions

Monday, 25th June - 10:55 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 87

Prof. Matthias Schwab [1]

1. *Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and Department of Clinical Pharmacology, University Hospital Tuebingen, Tuebingen, Germany*

The goal of personalized medicine is to provide individualized treatment and to predict the clinical outcome of different treatments in different patients. Pharmacogenomics (PGx) is one of the core elements in personalized medicine. The basic concept is that interindividual variability in drug response is a consequence of multiple factors, including genomics, epigenomics, the environment and a patient's characteristics, such as gender, age and/or concomitant medication. PGx research has led to fundamental discoveries in the last decade, and a large resource of PGx traits has been generated in which variation in the gene sequence and/or variation in the expression of genes involved in the metabolism, transport and other drug targets are associated with alterations in drug response. Interindividual variability of expression and function with consequences on drug response is not only affected by genetic factors (e.g. clinical examples are the cancer drugs thiopurines, tamoxifen, methotrexate, irinotecan)but could be also explained by epigenomics (DNA methylation, histone modifications, regulation by miRNA). DNA hypermethylation results in gene silencing by direct inhibition of transcription-factor binding or by recruitment of methylated DNA-binding proteins. There is proof of principle for the clinical value of methylation markers for classification, prognosis and prediction of therapeutic response, and tissue-specific methylation alters the expression of selected ADME genes (Fisel *et al.* Clin Pharmacol Ther 2016, Clin Transl Sci 2018 in press). The large-scale, systematic epigenomic equivalents of GWAS, termed epigenome-wide associations studies (EWAS), are promising tools to determine specific drug-related phenotypes attributable to interindividual epigenomic variation. The new generation of *-Omics* technologies permits assessment of the entirety of the components of biological systems and produces an explosion of data and a major shift in our concepts of disease. These technologies will likely shape the future of health care. One aspect of these advances is that the data generated document the uniqueness of each human being in regard to disease risk and treatment response. These developments have reemphasized the concept of personalized medicine.

The work is supported in part by the Robert Bosch Stiftung, Stuttgart, Germany

How can dendrimers contribute to precision/personalized medicine?

Monday, 25th June - 11:35 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 172

Prof. Anne-marie Caminade [1]

1. CNRS-LCC TOULOUSE

Dendrimers [1] are perfectly defined hyperbranched nanomolecules, which possess many biological properties [2]. The advantages of using dendrimers in the context of precision/personalized medicine will be emphasized in particular through two examples:

* Dendrimers can trigger the human immune system (Figure 1), and induce an anti-inflammatory response [3], with potential uses against Rheumatoid Arthritis [4], and Multiple Sclerosis [5].

* Dendrimers can be used for improving the sensitivity of biosensors for multiplexing technologies (Figure 2), for choosing the best personalized treatment to prescribe [6].

[1] Dendrimers. Towards Catalytic, Material and Biomedical Uses. Caminade A.M., Turrin C.O., Laurent R., Ouali A., Delavaux-Nicot B, Eds. Wiley & Sons, Chichester (UK) **2011**.

[2] a) Dendrimers in combination with natural products and analogues as anti-cancer agents. Mignani S., Rodrigues J., Tomas H., Zablocka M., Shi X., Caminade A.M., Majoral J.P. *Chem. Soc. Rev.* **2018**, *47*, 514; b) Phosphorous Dendrimers in Biology and Nanomedicine: Syntheses, Characterization, and Properties. Caminade A.M., Turrin C.O., Majoral J.P., Eds. Pan Stanford, **2018**.

[3] The key role of the scaffold on the efficiency of dendrimer nanodrugs. Caminade A.M., Fruchon S., Turrin C.O., Poupot M., Ouali A., Maraval A., Garzoni M., Maly M., Furer V., Kovalenko V., Majoral J.P., Pavan G.M., Poupot R. *Nature Comm.* **2015**, *6*, 7722

[4] A phosphorus-based dendrimer targets inflammation and osteoclastogenesis in experimental arthritis. Hayder M., Poupot M., Baron M., Nigon D., Turrin C.O., Caminade A.M., Majoral J.P., Eisenberg R.A., Fournié J.J., Cantagrel A., Poupot R., Davignon J.L. *Science Transl. Med.***2011**, *3*, 81ra35

[5] Phosphorus-based dendrimer ABP treats neuroinflammation by promoting IL-10-producing CD4+ T cells. Hayder M., Varilh M., Turrin C.O., Saoudi A., Caminade A.M., Poupot R., Liblau R. *Biomacromolecules***2015**, *16*, 3425

[6] a) Dendrimeric coating of glass slides for sensitive DNA microarrays analysis. Le Berre V., Trevisiol E., Dagkessamanskaia A., Sokol S., Caminade A.M., Majoral J.P., Meunier B., François J. *Nucleic Acids Res.* **2003**, *31*, e88.1-e88.8; b) Multiplexing technology for *in vitro* diagnosis of pathogens: the key contribution of phosphorus dendrimers. Majoral J.P., François J.M., Fabre R., Senescau A., Caminade A.M., *Science China Mater.* **2018***in press*; c) Dendris: http://www.dendris.fr/

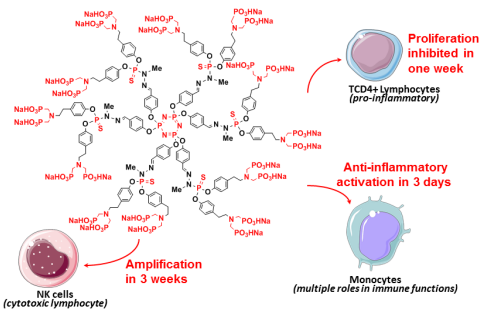


Figure 1.png

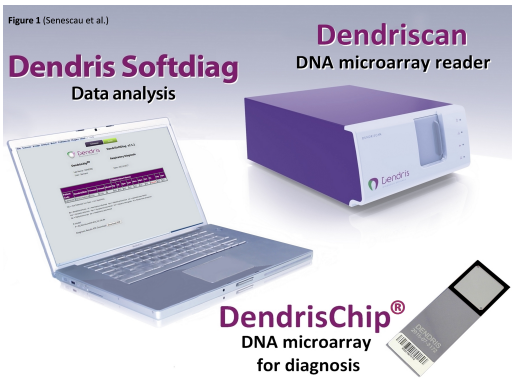


Figure 2 dendris.png

Novel Hot Spot Mutations in BCR-ABL1: a Personalised Medicine Approach in Chronic Myeloid Leukaemia

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 36

Dr. Erik Laurini [1], ***Dr. Suzana Aulic*** [1], ***Dr. Domenico Marson*** [1], ***Prof. Maurizio Fermeglia*** [1], ***Prof. Sabrina Pricl*** [1]

1. *University of Trieste*

Introduction

Acquisition of mutations in the BCR-ABL1 kinase domain (KD) is frequently associated with tyrosine kinase inhibitor (TKI) failure in chronic myeloid leukemia (CML). Recently, we revealed a novel mutation "hot-spot" in the BCR-ABL1 KD region (residues 295 – 312), associated with high resistance and poor clinical outcomes (Pricl S. et al., Molecular dynamics reveal BCR-ABL1 polymutants as a unique mechanism of resistance to PAN-BCR-ABL1 kinase inhibitor therapy. Proc Natl Acad Sci U S A. 2014 Mar 4;111(9):3550-5).

Here we present an integrated structural, computational, and molecular biology approach to understand the eventual role of the newly reported hot-spot mutations of the BCR-ABL1 KD in TKI resistance observed in CML patients.

Methods

We carried out our investigation using a "two-tier level" investigation: isolated KDs and SH2-linker-SH3-KD (SSKD) BCR-ABL1 constructs. Proteins structure, stability, drug binding and activity were studied by computational/structural (SAXS) biology, isothermal titration calorimetry, surface plasmon resonance, and *in vitro* kinase assays.

Results

Our findings demonstrate that each single hot-spot mutation exerts different effects on the protein structure, thermodynamic stability, ability to bind specific TKIs (e.g., imatinib, dasatinib, and ponatinib), and kinase activity. Moreover, the study reveals that 1) the use of isolated KD constructs might not be appropriated, 2) the drug residence time plays a major role in the presence of some kinase variants, and 3) the kinase activity of mutant BCR-ABL1 does not always correlate with TKI resistance.

Discussion

Our results show the potential of an inegrated, personalised medicine approach to TKI-resistant CML and provide a strategy that could improve clinical outcomes for CML patients. Characterizing drug resistance that is driven by mechanisms outside of the primary drug target is indeed quite difficult and time-consuming. Yet, the detailed knowledge of the likely escape mechanisms for a given therapy may impact drug selection and the sequencing of active targeted agents. And this, ultimately, will move cancer targeted therapy to the next level, bringing another round of fundamental change to the practice of oncology.

Cluster analysis of oncogenes associated with colorectal cancer

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 128

Dr. Dmitriy Babenko [1], ***Mrs. Yelena Babenko*** [1]

1. *Karaganda State Medical University*

Background: Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide and accounts for over 9% of all cancer cases diagnosed in 2012 (Ferlay,J. et al.,2012). The etiological factors and pathogenic mechanisms underlying CRC development appear to be complex and heterogeneous. Up to 35% of CRC cases are estimated to be attributable to genetic factors (Lichtenstein,P. et al.,2000). Today, gene discovery efforts have identified many CRC susceptibility genes and several molecular pathways have been described, such as the chromosomal instability, the microsatellite instability, and the CpG island methylator phenotype pathways (Bogaert,J. et al.,2014). The aim of this study was to perform clustering analysis on oncogenes associated with CRC.

Methods: Thirteen sources, including GWAS, ClinVar, UniProt, Cosmic, HGMD, malacards.org, targetvalidation.org and others, have been used to choose gene associated with CRC. To estimate the measurement of the association of genes to cancer, the OncoScore R/Bioconductor package has been used. Integrative GeneCards® database has been used to obtain comprehensive information for the oncogenes. The combination of BiologicalProcesses, CellularComponents, MolecularFunctions and Pathways data formed a gene profile in binary format that was used for clustering analysis. Minimum spanning trees (MST) has been generated with SeqSphere+ software (Ridom).

Results: Of 1708 found genes associated with CRC, 835 (48.9%) protein coding genes have been assigned as oncogenes based on OncoScore (> 25). 9906 unique parameters have been totally determined for the oncogenes, including 5135 biological processes, 668 cellular components, 1169 Molecular functions and 2934 pathways. MST on 835 genes have revealed cluster-like structure with 3 major and several minor clusters (figure 1). The most associated with CRC genes (top 10 genes from different databases) were distributed across different clusters (shown in red). Data of some clusters are listed in Table 1.

Conclusions: Cluster analysis of oncogene demonstrated cluster-like (grouped) structure on biological process, molecular functions pathways and cell localization data. Cluster forming gene had low involvement in various biological processes and metabolic pathways, although, with a sufficiently high oncogenic potential. The most associated with CRC genes were located far from the cluster center of with high involvement in various biological processes and metabolic pathways.

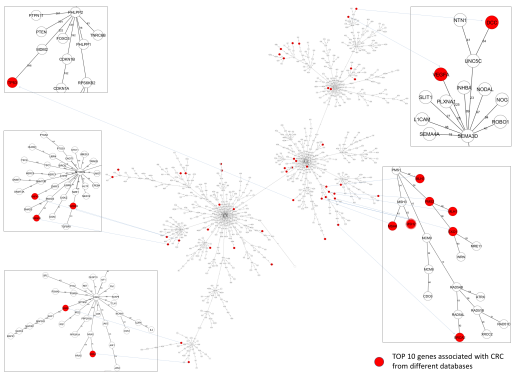


Figure 1. clustering of oncogenes associated with crc.png

Table 1. Informatin about cluster forming gene and top10 oncogenes associated with colorectal cancer

genes	Chromosome	Strand	# BiologicalProcesses	#CellularComponents	# MolecularFunctions	# Pathways	OncoScore	Database(s) where gene is Top10
Cluster forming gene								
MYCBP2	*13*	*Minus*	*3*	*3*	*8*	*1*	*81.3*	
TOP10 gene								
RNF43	*17*	*Minus*	*6*	*8*	*6*	*10*	*78.9*	*MSKCancerCell2018*
TGFBR2	*3*	*Plus*	*87*	*12*	*17*	*83*	*41.6*	*Cosmic*
SMAD4	*18*	*Plus*	*83*	*11*	*23*	*98*	*38.7*	*MSKCancerCell2018 MSKCCGenomeBio2014 Cosmic*
Cluster forming gene								
KSR2	*12*	*Minus*	*6*	*3*	*8*	*59*	*30.4*	
TOP10 gene								
BRAF	*7*	*Minus*	*43*	*10*	*15*	*232*	*86.9*	*malacards.org targetvalidation.org MSKCancerCell2018 cancergenomeinterpreter.org uniprot.org Cosmic*
KRAS	*12*	*Minus*	*37*	*8*	*8*	*348*	*88.7*	*CellReports2016 GenentechNature2012 MSKCancerCell2018 TCGANature2012 MSKCCGenomeBio2014 Cosmic*
Cluster forming gene								
PHLPP2	*16*	*Minus*	*3*	*6*	*8*	*21*	*62.6*	
TOP10 gene								
TP53	*17*	*Minus*	*85*	*18*	*34*	*255*	*90.5*	*CellReports2016 GenentechNature2012 MSKCancerCell2018 TCGANature2012 MSKCCGenomeBio2014 Clinvar Cosmic*
Cluster forming gene								
PMS1	*2*	*Plus*	*4*	*2*	*2*	*1*	*57.1*	
TOP10 gene								
MLH3	*14*	*Minus*	*8*	*6*	*8*	*4*	*53.2*	*uniprot.org HGMDpro*
MLH1	*3*	*Plus*	*28*	*11*	*8*	*27*	*84.3*	*cancergenomeinterpreter.org Clinvar uniprot.org HGMDpro*
EXO1	*1*	*Plus*	*16*	*4*	*16*	*26*	*44.1*	*HGMDpro*
MSH6	*2*	*Plus*	*16*	*8*	*19*	*18*	*79*	*Clinvar uniprot.org HGMDpro*
MSH2	*2*	*Plus*	*30*	*7*	*27*	*26*	*80.7*	*cancergenomeinterpreter.org Clinvar uniprot.org HGMDpro*
Cluster forming gene								
SEMA3D	*7*	*Minus*	*4*	*3*	*1*	*1*	*25.3*	
TOP10 gene								
DCC	*18*	*Plus*	*15*	*5*	*3*	*19*	*48.2*	*malacards.org*
VEGFA	*6*	*Plus*	*97*	*8*	*13*	*108*	*42.8*	*targetvalidation.org*

Table 1. informatin about cluster forming gene and top10 oncogenes associated with colorectal cancer.png

Influence of combined CYP3A4 and CYP3A5 single-nucleotide polymorphisms on tacrolimus exposure in kidney transplant recipients

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 55

Ms. Ibtissem Hannachi [1], Dr. Zohra CHADLI [1], Dr. Emna Kerkeni [2], Dr. Amel Chaabane [1], Dr. Nadia Ben Fredj [1], Prof. Naceur Boughattas [2], Prof. Karim Aouam [1]

1. *Pharmacology Department, University Hospital, Monastir, Tunisia. Faculty of Medicine, University of Monastir, Tunisia.,* ***2.*** *Pharmacology Department, Faculty of Medicine, University of Monastir, Tunisia.*

Tacrolimus (Tac), an immunosuppressant used for the prevention of graft rejection in kidney transplant patients, is characterized by a high interindividual variability of its pharmacokinetics. It is metabolized specifically by the CYP3A isoenzyme: CYP3A4 and CYP3A5.The present study investigated in Tunisian renal transplant patients, the genetic polymorphisms of *CYP3A4*1B*-392A>G, *CYP34*22*15389C>T and *CYP3A5*3*6986A>G, and their influence on tacrolimus pharmacokinetics during early and late post-transplant (PT) phases
The present study investigated in Tunisian renal transplant patients, the genetic polymorphisms of *CYP3A4*1B*-392A>G, *CYP34*22*15389C>T and *CYP3A5*3*6986A>G, and their influence on tacrolimus pharmacokinetics during early and late post-transplant (PT) phases.

Methods

We included adult Tunisian patients having received Tac for de novo kidney grafts and undergone a therapeutic drug monitoring (TDM) of Tac by C_0 monitoring during early (1 to 90 days) and late (over 90 days) PT phases. The genomic DNA was extracted from peripheral blood mononuclear cells using a salting-out procedure. *CYP3A4* and *CYP3A5* genotyping was performed using
polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP).

Results

Seventy-eight patients were enrolled in this study. During the early PT phase, only the CYP3A5*3 and the CYP3A4*22 polymorphisms correlate significantly with Tac dose-normalized C_0 (C_0/D ratio). During the late and all PT phases, only the CYP3A4*1B polymorphism correlates significantly with Tac C_0/D ratio. The mean daily doses (mg/kg) matching therapeutic C_0, regardless of the *CYP3A genotypes*were 0.68 ± 0.2 and 1.09± 0.17 , during early and late PT phase, respectively.

Conclusions

Our data support a critical role of the *CYP3A4*1B*, *CYP34*22* and *CYP3A5*3*polymorphisms on the variation of Tac exposure during the early and the late PT phase, respectively. The establishment of customized Tac doses, according to *CYP3A4*/*CYP3A5*genotype combination and the PT time, may allow preventing graft rejection and improving the safety profile of this drug.

Transient neonatal diabetes : multilocus methylation defects associated with novel ZFP57 mutation

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 155

Ms. Ameni Touati [1], Dr. Javier Errea [2], Prof. Sonia Nouri [3], Dr. Arreta Pereda [2], Dr. Aida Guith [3], Prof. Nabiha Mahdhaoui [3], Prof. Ali Saad [1], Prof. Guiomar Perez De Nanclares [2], Prof. Dorra H'mida [1]

1. *Farhat HACHED university hospital . department of cytogenetics, molecular genetics and reproductive biology,* ***2.*** *Molecular (Epi)Genetic Lab, OSI Araba University Hospital, Vitoria Gasteiz, Spain.,* ***3.*** *Farhat HACHED university hospital . department of neonatology*

Introduction: Transient neonatal diabetes (TND) is a rare imprinting disorder. Affected infants are often found to be hyperglycemic during the first 6 months of life. TND molecular aetiology is attributable to defects causing overexpression of the paternally inherited *PLAGL1* and*HYMAI* genes on chromosome 6q24. Over 50% of patients with hypomethylation at the TNDM locus have additional hypomethylation of other imprinted genes (multilocus imprinting disturbances, MLID). In a proportion of these patients, recessive mutations in *ZFP57* gene are identified.

Methods: We report an affected Tunisian male child who had hyperglycemia and mild dysmorphism consisting in macrostomia and macroglossia. We studied at first the methylation status of the paternally 6q24 imprinted locus. Then, in order to investigate MLID, 5 maternally (7q32, 7p12, 11p15.5, 15q11-13 and 20q13.3) and 3 paternally (11p15.5, 14q32 and 15q11-13) imprinted loci were analyzed.

Results: Methylation testing revealed, at 6q24 locus, a complete hypomethylation confirming the diagnosis of TND. Additionally, the patient was totally hypomethylated at 7p12 locus and partially hypomethylated at 7q32 and 20q13.3 loci. Coding regions of*ZFP57*, with intron-exon boundaries, were sequenced in our TND-MLID patient and his parents. The patient was carrier of a novel nonsense mutation (c.373C>T; p.Arg125*). The truncating substitution was heterozygously found in the parents.

Discussion :ZFP57 encodes a zinc-finger transcription factor expressed in early development. It plays a critical role in the maintenance of DNA methylation at multiple imprinting control regions. Here we provide additional support of the role of *ZFP57* gene as an important genetic determinant for the diagnosis of TND-MLID is underlined.

Targeting the JNK-JUN pathway to reduce phenotypic plasticity and overcome therapy resistance in metastatic melanoma

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 86

Dr. Petranel Ferrao [1]

1. *Institute for Breathing and Sleep*

Introduction

Patients with metastatic melanoma have displayed remarkable responses to targeted and immune therapies that have been approved for treatment in recent years. However, responses to targeted therapies are partial or short-lived in the majority of patients, and responses to immune modulating therapies are limited to a small proportion of patients. Combination treatments with therapies that are able to overcome the inherent and early adaptive resistance mechanisms will provide more durable responses and survival benefits for melanoma patients.

Methods and Results

Pharmaco-genomic analysis identified activation of the JNK-JUN pathway as a key mechanism of cell survival, drug resistance and EMT-like phenotype-switching during early drug adaptation to treatment with BRAF/MEK/ERK inhibitors (1). Combination treatment with JNK inhibitors or siRNA-mediated reduction in c-JUN levels was sufficient to overcome inherent and early adaptive resistance to inhibition of the RAF-MEK-ERK pathway (1). Scheduling of JNK inhibitor combination after early adaptive changes that up-regulated c-JUN resulted in enhanced cell killing (1) There was a strong correlation in multiple melanoma microarray datasets between high *JUN* expression and a mesenchymal-like phenotype (1). A significant correlation was also detected between high *JUN* expression and high expression of CD274 encoding PD-L1 (2).

Discussion

Targeting the JNK-JUN pathway in melanoma offers the potential to overcome therapy resistance to RAF-MEK-ERK pathway targeted therapies, while simultaneously addressing phenotypic changes that have been linked to immune evasion and metastasis promoting properties (3). Hence, pre-clinical optimisation of drug candidates and scheduling of JNK-JUN pathway inhibitor treatments will be critical for exploiting the changes associated with phenotypic plasticity, to obtain more effective and durable responses to targeted and/or immune therapies in the treatment of melanoma.

1. R Ramsdale, R Jorissen, *et .al* .,P T Ferrao. (2015). *Science Signaling*8: 390 ra82.

2. P T C Ferrao (2016) International (PCT) Patent Application No. PCT/AU/2016/050075 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2016123679

3. P T Ferrao. (2016) *Molecular and Cellular Oncology*. 3(3): e1128515.

Pharmacogenomics of Sickle Cell Disease: Pain and Drug metabolism associated Gene Variants, and hydroxyurea-induced miRNAs

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 163

Ms. Khuthala Mnika [1], ***Prof. Wonkam Ambroise*** [1], ***Dr. Emile Chimusa*** [1], ***Prof. Collet Dandara*** [1], ***Dr. Shaheen Mowla*** [1]

1. *University of Cape Town*

Background: The major therapeutic benefit of hydroxyurea (HU), the only FDA-approved pharmacologic treatment for sickle cell disease (SCD), is directly related to fetal hemoglobin (HbF) production that leads to significant reduction of morbidity and mortality. However, potential adverse effects such as infertility, susceptibility to infections, or teratogenic effect have been subject for concern. It is therefore important to gain a better understanding of genetic variants affecting the predisposition to specific complications such as stroke and acute chest syndrome, and polymorphisms affecting susceptibility to pain, as well as the pharmacogenomics of commonly prescribed treatments such as HU, malaria prophylaxis and pain medication for future precision medicine in SCD. In this study we aim to investigate 1) Drug Metabolizing Enzyme and Transporter (DMET) genes variants, and 2) to study changes in miRNA expression linked to treatment with HU, in Sickle Cell Disease.

Objectives: To investigate variants of Drug Metabolizing Enzyme and Transporter (DMET) Genes in SCD; to determine the*in vivo*post-transcriptomic profile of hydroxyurea-induced miRNA in SCD patients in Cape Town; to determine the *in vitro* post-transcriptomic profile of hydroxyurea-induced miRNA in human erythroid progenitor cells derived from umbilical cord CD34+ stem cells.

Methods: We will interrogate available exomes data of 150 SCD opioid and hydroxyurea urea naive patients and 50 population-matched controls and determine the differential minor allele frequencies. Analyses of the available miRNA profile (Human miRNA microarrays) from the transcriptome data, pre and post administration of HU will be conducted. In addition, we will treat human erythroid progenitor cells derived from umbilical cord CD34+ stem cells with HU and investigate the molecular mechanisms of HbF induction through miRNA regulation. Lastly, we will compare the outcomes from *in vivo* and *in vitro* experiments, in order to determine that are constantly differentially expressed under HU exposure.

Expected outcomes: This study will help in identifying miRNAs that can be explored as part of therapeutic strategies for sickle cell patients. It will also contribute in the development of a pharmacogenomics model for SCD in the African population.

The polymorphism rs6918289 located in the downstream region of the TREM2 gene is associated with TNF-α levels and IMT-F

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 114

Mrs. Vesna Gorenjak [1], ***Dr. Alex-Ander Aldasoro Arguinano*** [1], ***Dr. Sébastien Dadé*** [1], ***Dr. Maria Stathopoulou*** [1], ***Dr. Dwaine Vance*** [2], ***Ms. Christine Masson*** [1], ***Dr. Sophie Visvikis-Siest*** [1]

1. *INSERM UMR U1122,* ***2.*** *Randox*

Introduction

Triggering receptor expressed on myeloid cells 2 (TREM2) is known for its anti-inflammatory properties during the immune response. Moreover, TREM2 levels have been observed to affect plasma levels of TNF-α and plaque stability in symptomatic and asymptomatic patients with carotid stenosis. In this study, we investigated polymorphisms located in the *TREM2* gene region and their association with TNF-α levels and the intima media thickness of the femoral artery in healthy individuals.

Methods

Discovery population consisted of **139** healthy children from the STANISLAS Family Study (SFS). Five readily available SNPs located in TREM-2 region (rs7748777, rs6918289, rs7759295, rs9357347 and rs6915083 available in the genome-wide scan IlluminaHuman CNV370-Duo array) were analyzed for associations with TNF-α levels, using the R package GWAF (Genome-Wide Association/Interaction Analysis and Rare Variant analysis with Family Data). After performing initial association analysis, the polymorphism rs6918289 was *de novo* genotyped in 393 adults and 277 more children of SFS and in an independent replication population (*n*=**916**). *De novo* genotyping of rs6918289 was conducted by Laboratory of the Government Chemist (LGC) using a PCR-based KASP assay. The association of the rs6918289 with TNF-α plasma levels was assessed separately in the total individuals of SFS (children and adults combined; *n*=**809**) and in the replication population (*n*=916). A sub-group of **350** individuals, consisting of adults and children from the SFS population was used to identify associations between intima media thickness of the femoral artery (IMT-F) and rs6918289.

Results

Our results suggest that the minor allele (T) of the rs6918289 is positively associated with elevated plasma levels of TNF-α in the discovery population (*P*=0.0026, β=0.13, *SE*=0.04) (Figure 1). Similar results were found in the replication population (*P*=0.023, β=0.202, *SE*=0.09). Additionally, rs6918289 was associated with IMT-F in the discovery cohort (*P*=0.026, β=0.02, *SE*=0.009).

Figure 1: Mean values of TNF-α levels according to the different genotypes of rs6918289 (GG vs TG vs TT) in the STANISLAS population. Thin bars show SE.

Discussion

These results indicate that rs6918289 may be considered as a risk factor for inflammatory diseases and could be used in personalized medicine for patients diagnosed with chronic inflammatory-related conditions such as atherosclerosis.

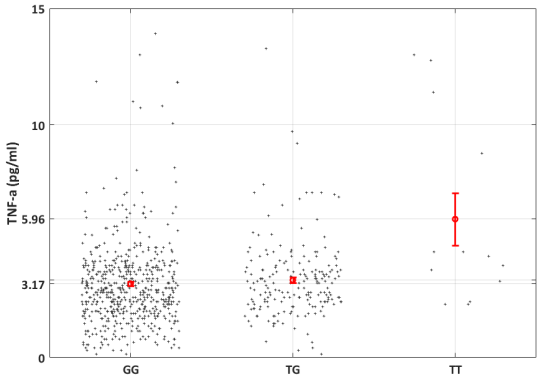


Figure 1.png

Development of microRNA biomarkers for predicting toxicities of selective COX-2 NSAIDs using Daphnia model

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 112

Mr. Myung-Gyun Kang [1], ***Dr. Bosun Kwon*** [2], ***Ms. Yoonjung Hong*** [3], ***Dr. Ryeo-ok Kim*** [4]

1. *Korea Institute of Toxicology,* ***2.*** *Winnova Co. and Wooridul Huebrain,* ***3.*** *Winnova Co.,* ***4.*** *Sangmyung University*

Non-steroidal anti-inflammatory drugs (NSAIDs) target the cyclooxygenase (COX) isoforms including COX-1, COX-2 or COX-3 in human and reduce pain, fever, and inflammation by inhibiting prostaglandin formation. Although NSAIDs have been extensively prescribed all over the world, NSAIDs in overdose were reported to induce various side effects on non-target tissues. Especially, many COX-2 inhibition drugs have been withdrawn from the markets due to their safety concerns. Therefore, it is important to understand toxicological mechanisms modulated by selective COX-2 inhibitors for prediction of their adverse effects. In this study, we used daphnia as test organism because they have been widely used in research fields such as toxicology and genomics, and their eicosanoids biosynthesis pathway regulated by COX was recently identified. Daphnia has only one isoform of COX while some genes such as prostaglandin D_2(PGD_2) synthase and thromboxane A_2 (TXA_2) synthase exist in two isoforms unlike those in human. To compare molecular responses changed by non-selective inhibitors, preferential COX-2 inhibitors, and selective COX-2 inhibitor, we analyzed transcriptional levels of several genes involved in eicosanoids biosynthesis pathway triggered by COX in daphnia exposed to 7 different NSAIDs. As a result, Celecoxib (selective COX-2 inhibitor) induced most genes while ibuprofen (non-selective inhibitor) and Nimesulide (preferential COX-2 inhibitor) activated specific genes in a dose- and time-dependent manner, indicating selective COX-2 inhibitor strongly modulates eicosanoids biosynthesis pathway compared to other NSAIDs although we haven't yet confirmed whether it inhibits COX enzyme activity in daphnia. And also we found that Diclofenac (non-selective inhibitor) shows similar expression patterns to Celecoxib. So we carried out microRNA sequencing using small RNA extracted from daphnia exposed to Celecoxib and Diclofenac. In fact, microRNAs are associated with various molecular mechanisms and regarded as promising biomarkers for a range of diseases. After analyzing microRNA sequencing data, we will elucidate toxicological mechanisms and find novel biomarkers for predicting toxicity by selective COX-2 inhibitor.

Pharmacogenetics of P450 CYP3A4 and CYP3A5 in the Tunisian population: Clinical application with tacrolimus

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 53

Ms. Ibtissem Hannachi [1], Dr. Zohra CHADLI [1], Dr. Emna Kerkeni [1], Dr. Amel Chaabane [1], Dr. Nadia Ben Fredj [1], Prof. Naceur Boughattas [2], Prof. Karim Aouam [1]

1. *Pharmacology Department, University Hospital, Monastir, Tunisia. Faculty of Medicine, University of Monastir, Tunisia.,* ***2.*** *Pharmacology Department, Faculty of Medicine, University of Monastir, Tunisia.*

Human cytochrome P450 (CYP), particularly CYP3A4 and CYP3A5 is mainly responsible for the metabolism of several drugs including Tacrolimus. Significant interracial/interethnic variation in the expression and function of CYP3A5 and CYP3A4 is caused by Single Nucleotide Polymorphisms (SNPs) of genes encoding these proteins. The present study investigated in Tunisian population, genetic polymorphisms of CYP3A4*1B -392A>G, CYP34*22 15389C>T and CYP3A5*3 6986A>G.

We included in this study, Tunisian healthy subjects and renal transplant recipients receiving tacrolimus. The genomic DNA was extracted from peripheral blood mononuclear cells using a salting-out procedure. CYP3A4 and CYP3A5 genotyping was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP). The results showed that the predominant alleles in Tunisian population are wild type of CYP3A4*1B (0.87), likewise CYP3A4*22 (0.975) and CYP3A5*3 (0.82). The genotype frequencies of CYP3A4*1B, CYP3A4*22 and CYP3A5*3 were found to be 3.9%, 0.0% and 69.5%, respectively. The genotype combination of CYP3A4*1B, CYP3A4*22 and CYP3A5*3 were made as follows: extensive metabolizers (EX) when harboring: CYP3A4*1B (*1/*1, *1/*B or *1B/*1B), CYP3A4*22 (*1/*1) and CYP3A5*3 (*1/*1 or *1/*3); intermediate metabolizers (IM) : CYP3A4*1B (*1/*1 or *1/*1B), CYP3A4*22 (*1/*1 or *1/22) and CYP3A5*3 (*1/*1, *1/*3 or *3/*3) and low metabolizers (SM) : CYP3A4*1B (*1/*1); CYP3A4*22 : (*22/*22 or *1/*22) and CYP3A5*3 (*3/*3). The results showed that Tunisian population are intermediate metabolizers and most similar to Caucasians.

The genetic background of these enzymes CYP3A4*1B, CYP3A4*22 and CYP3A5*3 in this study are important in the prescription of personalized medicine

Analysis of the expression and colocalization study of CD44 And CD74 receptors expressed on human lung cancer derived cell.

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 13

Dr. Waleed Al abdulmonem [1], ***Dr. Hussain Alssadh*** [2]

1. *Qassim University,* ***2.*** *University of Essex*

Several studies have shown that CD44 and CD74 are overexpressedand dysregulated in various type of cancer, including lung cancer, breast cancerand prostate cancer. There selective expression in tumours is known to activatesignalling mechanisms that drive tumour progression. **CD44** is atransmembrane glycoprotein molecule that functions in cell proliferation,migration and adhesion and also acts as a receptor for hyaluronic acid. **CD74**is a non-polymorphic glycoprotein that functions in regulating the traffickingof MHC class II protein (Karakikes et al, 2012) and also serves as the receptorfor macrophage inhibitory factor (MIF). The MIF/CD74 receptor complex requiresCD44 as the signalling component. We have employedflow cytometry and to examine non-small cell lung cancer cell line, A549 forCD74 and CD44. We observed that CD44 was higher than CD74. UsingCo-localization experiments and bio imaging we performed quantitativevariations of CD74 and CD44 receptors in order to evaluate their association incytoplasmic compartments. We conclude that the two receptors CD44 and CD74 arenot colocalized in this cell line. This suggests that they modulate functionsas separate entities on non-small lung cell cancer.

The Diagenode Epigenetics Custom Service: Complete workflows for genome-scale DNA methylation and histone marks analysis

Monday, 25th June - 14:00 - Poster Session - Main hall - Poster - Abstract ID: 184

Dr. Matteo Tosolini [1]

1. *Diagenode*

Epigenetics is crucial for the regulation of gene expression and has broad relevance in biological processes like development, disease and response to the environment. For more than 10 years Diagenode has been developing innovative tools to study epigenetic marks such as post-translational modifications of histones and DNA methylation. We are now utilizing our expertise by offering custom services. Our services include full workflows for ChIP-sequencing as well as reduced representation bisulfite sequencing (RRBS) with our new optimized “Premium RRBS™ technology. In addition, we also offer bioinformatic analysis of your results, both standard and customized. The Diagenode Epigenetics Custom Services helps you to complete your epigenetics workflow from your starting biological material to your final results.

How to Consider Rare Genetic Variants in Personalized Drug Therapy

Monday, 25th June - 15:00 - Pharmacogenomics & Epigenomics Workshop - Amphitheater - Workshop - Abstract ID: 90

Mr. Yitian Zhou [1], Dr. Souren Mkrtchian [1], Prof. Masahiro Hiratsuka [2], Prof. Magnus Ingelman-sundberg [1], Dr. Volker Lauschke [1]

1. *Karolinska Institutet,* ***2.*** *Tohoku University*

Variability in genes implicated in drug pharmacokinetics or drug response can modulate treatment efficacy or predispose to adverse drug reactions. Research in the last decades revealed a multitude of associations between genotype and drug response, some of which are now included in drug labels. However, in recent years it became evident that the vast majority of the number of genetic variants in genes of importance for drug metabolism, transport and response are rare, with minor allele frequencies <1%.

To understand the global importance of rare pharmacogenetic gene variants, we mapped the genetic variability in 208 pharmacogenes by analyzing exome sequencing data from 60,706 unrelated individuals. To estimate the importance of rare and common genetic variants we developed a functionality prediction framework optimized for pharmacogenetic assessments based on experimental functionality data from 240 pharmacogenetic variant alleles in 22 different ADME genes. Our model achieved 92% sensitivity and 95% specificity for loss-of-function and functionally neutral variants, respectively.

Our analyses reveal that rare pharmacogenetic variants were strongly enriched in mutations predicted to cause functional alterations. For more than half of the pharmacogenes, rare variants account for the entire genetic variability. Each individual harbored on average a total of 40.6 putatively functional variants, rare variants accounting for 10.8% of these. Overall, the contribution of rare variants was found to be highly gene- and drug-specific. Using warfarin, simvastatin, voriconazole, olanzapine and irinotecan as examples, we conclude that rare genetic variants likely account for a substantial part of the unexplained inter-individual differences in drug metabolism phenotypes.

The abovementioned improvements in the performance of computational algorithms to reliably flag functionally deleterious and neutral variants raise hopes that predictions regarding the functionally most important mutations in the different genes of importance for a respective drug treatment can be made based on whole exome or whole genome sequencing data (Figure 1). While multiple challenges still need to be overcome, we suggest that computationally interpreted NGS-data can be of great importance for decision-making regarding choice of drug therapy and dosing regimen in the clinical setting.

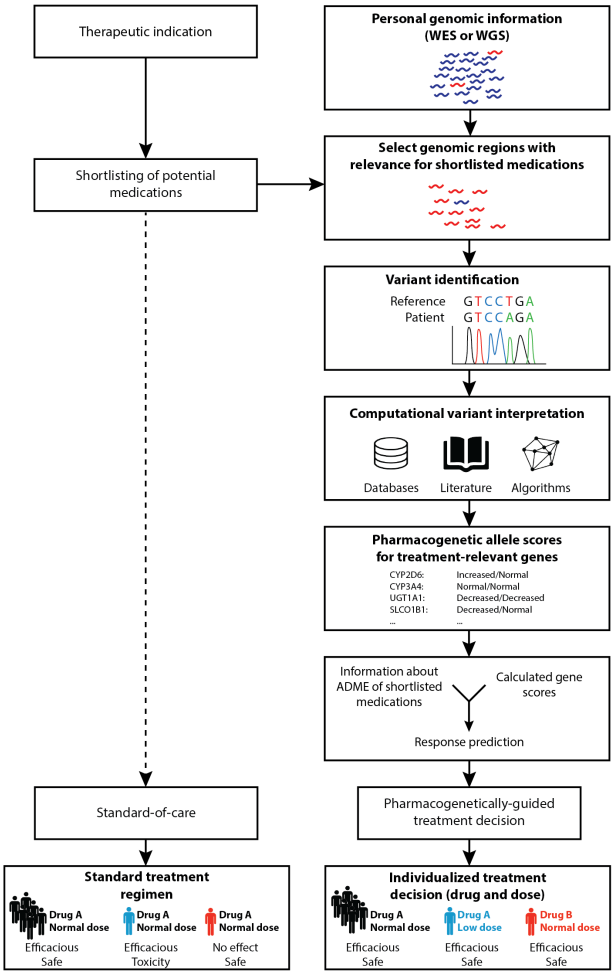

Therapeutic indication
Shortlisting of potential medications
Standard-of-care
Standard treatment regimen
Drug A Normal dose
Drug A Normal dose
Drug A Normal dose
Efficacious Safe
Efficacious Toxicity
No effect Safe
Personal genomic information (WES or WGS)
Select genomic regions with relevance for shortlisted medications
Variant identification
Reference GTCCTGA
Patient GTCCAGA
Computational variant interpretation
Databases
Literature
Algorithms
Pharmacogenetic allele scores for treatment-relevant genes
CYP2D6: Increased/Normal
CYP3A4: Normal/Normal
UGT1A1: Decreased/Decreased
SLCO1B1: Decreased/Normal
Information about ADME of shortlisted medications
Calculated gene scores
Response prediction
Pharmacogenetically-guided treatment decision
Individualized treatment decision (drug and dose)
Drug A Normal dose
Drug A Low dose
Drug B Normal dose
Efficacious Safe
Efficacious Safe
Efficacious Safe

Fig1-01.png

Implementation of Pharmacogentics in clinical practice – The U-PGx project

Monday, 25th June - 15:20 - Pharmacogenomics & Epigenomics Workshop - Amphitheater - Workshop - Abstract ID: 182

Dr. Jesse Swen [1]

1. *Leiden University Medical Center*

Today, we are facing a paradigm shift in the way we manage and treat patients with complex diseases. The days of the “blockbuster drug” and treatment selection based on trial-and-error are rapidly coming to an end and pharmacogenetics (PGx) is starting to enter routine clinical practice. Implementing pharmacogenomics in the clinic, however, is not without its challenges. The Ubiquitous Pharmacogenomics consortium (U-PGx) will address major challenges and obstacles for implementation of PGx testing in patient care, taking into account the diversity of healthcare systems and citizens across Europe. Specifically, U-PGx will investigate if the emerging approach of pre-emptive genotyping of an entire panel of important PGx markers is cost-effective and results in a better outcome for patients. With the pre-emptive PGx testing approach data on multiple important pharmacogenes are collected prospectively and embedded into the patients’ electronic record. Typically, it alerts prescribers and pharmacists through electronic clinical decision support systems when a drug is ordered or dispensed for a patient with an at-risk genotype. The new model of personalised medicine through pre-emptive PGx-testing is tested at a large scale in seven existing European health care environments (The Netherlands, Spain, UK, Italy, Austria, Greece, Slovenia).

Pharmacogenomics of drug-induced liver injury

Monday, 25th June - 15:40 - Pharmacogenomics & Epigenomics Workshop - Amphitheater - Workshop - Abstract ID: 99

Prof. Ann Daly [1]

1. *Newcastle University*

Drug-induced liver injury (DILI) is a rare but serious adverse reaction with certain widely prescribed drugs and can result in liver failure. It is also a relatively common cause of attrition during drug development. Using genome-wide association studies, highly significant associations with particular HLA genotypes have been detected for idiosyncratic DILI with a number of specific drugs, for example flucloxacillin, co-amoxiclav and terbinafine. Examples of these associations and possible underlying mechanisms, including how these may relate to reported HLA associations for other types of adverse drug reactions, will be considered. Not all forms of idiosyncratic DILI show HLA gene associations. Genes relevant to the innate immune system and to drug disposition appear to represent additional risk factors for DILI but, as with the associations involving HLA, risk factors are mainly but not exclusively dependent on the individual drug. The genetic associations we have seen, involving both HLA and non-HLA genes, provide new insights into the underlying mechanisms for idiosyncratic DILI and may assist in the development of improved strategies for its prediction and diagnosis.

Genetic variability in organic cation transporter OCT1: a variance with clinical implication?

Monday, 25th June - 16:00 - Pharmacogenomics & Epigenomics Workshop - Amphitheater - Workshop - Abstract ID: 187

Prof. Mladen Tzvetkov [1]

1. *University Medical Center Greifswald*

OCT1 is by far the most strongly expressed uptake transporter of cationic and weekly basic drugs in the human liver. OCT1 is highly genetically variable. Approximately 1 in 11 Europeans and White Americans is a homozygous or compound-heterozygous carrier of loss or reduced function OCT1 alleles. These “poor OCT1 transporter” may have reduced hepatic uptake and/or impaired metabolism of some commonly used drugs like metformin, morphine, codeine, tramadol, sumatriptan, and fenoterol. Consequently, these individuals may have altered drug efficacy and may be at higher risk of toxicities. A recently published opinion paper of the International Transporter Consortium strongly suggested that OCT1 polymorphisms should be considered during drug development (https://doi.org/10.1002/cpt.1098). This talk will review the available data on the effects of heritable OCT1 deficiency on pharmacokinetics, efficacy, and toxicity of some commonly used drugs, will give an overview of the inter-ethnic differences in heritable OCT1 deficiency, and will critically discuss the possible applications of OCT1 genotyping in the clinical praxis.

Interindividual variability of hepatic membrane transporters and its impact on precision medicine

Monday, 25th June - 17:00 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 174

Prof. Anne Nies [1]

1. *Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany*

Precision medicine aims to identify factors that contribute to the interindividual variability in drug response. Drug effects essentially depend on the processes of absorption, distribution, metabolism and excretion of therapeutic compounds. It has been well established that hepatic membrane transporters are important determinants of the biliary elimination of endogenous compounds and various drugs. Examples of endogenous compounds are bile salts and bilirubin glucuronides whereas examples of drugs include the cholesterol-lowering statins and the anti-diabetic agent metformin. Several membrane transporters have been identified that mediate the sinusoidal uptake of these and other compounds into the hepatocytes (e.g. SLC10A1, SLCO1B1, SLCO1B3, SLCO2B1, SLC22A1, SLC22A7, SLC22A9) and the elimination of these or their metabolites across the canalicular membrane into bile (e.g. ABCB1, ABCC2, ABCG2). Functional genetic variants e.g. in *SLCO1B1* have been identified to be associated with simvastatin-induced myopathy.

Interindividual variability in expression of hepatic membrane transporters may affect response to drugs or predispose to the development of hepatic disorders such as acquired forms of intrahepatic cholestasis. We therefore investigated genetic variants and expression of hepatic transporters in a large normal liver tissue bank by next-generation sequencing, comprehensive transcriptome analysis and proteomics analysis. We demonstrated a considerable interindividual variety of protein expression for each transport protein in normal human liver. Moreover, absolute protein levels were much higher for the sinusoidal uptake transporters compared with the canalicular transporters. Several genetic variants were identified that affected protein expression of some transporters. In conclusion, variable membrane transporter expression may impair the hepatic elimination and response to a variety of drugs that depend on transporter-mediated biliary elimination.

The work is supported in part by the Robert Bosch Stiftung, Stuttgart, Germany.

DNA Methyltransferases Expression in Triple-negative Breast Cancer Predicts Sensitivity to Decitabine

Monday, 25th June - 17:35 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 106

Dr. Liewei Wang [1], ***Dr. Jia Yu*** [1]

1. *Mayo Clinic*

Introduction

Triple-negative breast cancer (TNBC) is a heterogeneous disease with poor prognosis and lacking targeted therapies especially in patients with chemotherapy resistant disease. Since DNA methylation-induced silencing of tumor suppressors is common in cancer, reversal of promoter DNA hypermethylation by decitabine (5-aza-2'-deoxycytidine), an FDA-approved DNA methyltransferase (DNMT) inhibitor, has proven effective in treating hematological neoplasms. However, its antitumor effect varies in solid tumors, stressing the importance of identifying biomarkers predictive of therapeutic response.

Methods

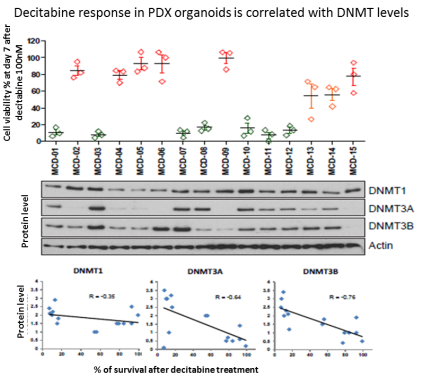
Breast cancer TNBC patient derived xenograft (PDX) models were used to determine correlation between DNMTs and decitabine response. Breast cancer cell lines, Hs 578T, BT-549 and MDA-MB-231 cells were used to perform in vitro experiments. To determine the decitabine effect on DNMTs, cells were treated with 100 nM of decitabine for 7 days, followed by determining DNMT levels and IP was performed to test decitabine induced DNMT ubiquitination. To understand the E3 ligase, TRAF6 effect, cells were transfected with TRAF6 siRNAs and DNMT levels, decitabine cytotoxicity as well as global DNA methylation was determined by Western blot analysis, MTS assay and blotting with anti-5-methylcytosine monoclonal antibody, respectively.

Results

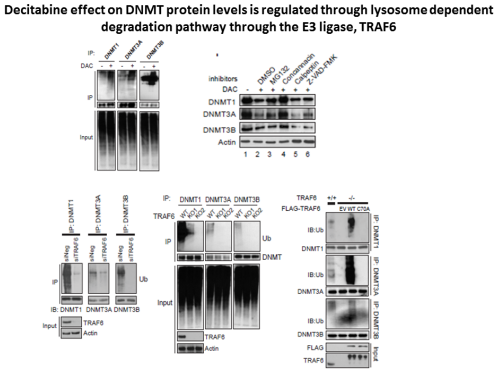
We showed that protein levels of DNMTs correlated with response to decitabine in TNBC patient derived xenograft (PDX) organoids, suggesting DNMT levels as potential biomarker of response. Furthermore, all three methytransferases, DNMT1/3A/3B, were degraded following low-concentration, long-term decitabine treatment both in vitro and in vivo. The DNMT proteins could be ubiquitinated by the E3 ligase, TNF receptor associated factor 6 (TRAF6), leading to lysosome-dependent degradation. Depletion of TRAF6 blocked decitabine-induced DNMT degradation, conferring resistance to decitabine.

Discussion

Our study suggests that decitabine induces degradation of DNMT1, DNMT3A and DNMT3B by TRAF6 through a lysosome dependent degradation pathway. This is one major mechanism by which decitabine inhibits tumor growth. DNMT protein levels might serve as a potential biomarker to guide the drug selection. Finally, TNBC PDX responded to decitabine regardless of chemotherapy response. Therefore, TNBC patients with high DNMT levels and resistance to standard chemotherapy may still benefit from decitabine. Future clinical studies are required development to test decitabine like drugs in high risk TNBC patients.



Slide1.png



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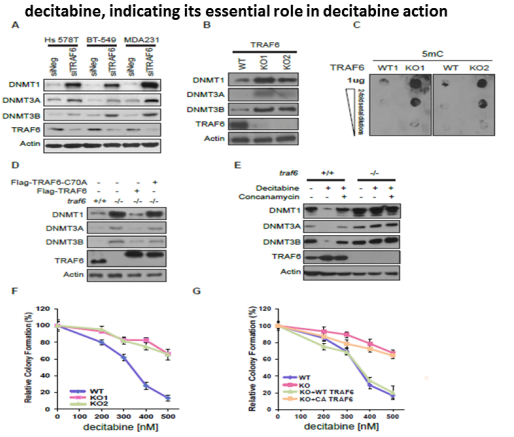


Slide3.png

Liquid biopsy: A new diagnostic concept in oncology

Tuesday, 26th June - 09:00 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 188

Prof. Klaus Pantel [1]

1. *University Medical Center Hamburg-Eppendorf*

“Liquid biopsy” was introduced as a new diagnostic concept in 2010 for the analysis of circulating tumor cells (CTCs) and has been now extended to material (in particular DNA) released by tumor cells in the peripheral blood of cancer patients. Over the past decade, various methods have been developed to detect CTCs and ctDNA in the peripheral blood of cancer patients. While reliable information can be easily obtained in patients with advanced disease, early stage cancer patients usually present with very low concentrations of CTCs and ctDNA. At present, most CTC assays rely on epithelial markers and the majority of CTCs detected are single isolated cells. The clinical relevance of ‘mesenchymal’ CTCs lacking any epithelial markers as well as CTC clusters are still under investigation. Although most published studies have been performed on patients with carcinomas and melanomas, CTCs have been also detected in the peripheral blood of patients with primary brain tumors (glioblastomas) despite the blood-brain barrier.

Liquid biopsy assays are currently being validated for early detection of cancer, which is supposed to reduce cancer related mortality. Despite remarkable progress, liquid biopsy-based detection of early stages of cancer remains a challenge, in particular in breast cancer. New blood-based biomarkers for early detection currently validated in clinical trials include miRNAs, exosomes and tumor-educated platelets.

In patients with diagnosed cancer, CTCs and ctDNA analyses can obtain independent information on prognosis in early and advanced stages of disease. In particular, CTC counts at initial diagnosis are able to refine the current risk stratification by TNM staging in early stage breast cancer. Moreover, early detection of relapse by sequential ctDNA (or CTCs) analysis of blood samples obtained post-surgery during the follow up is possible and may be used in future trials to stratify patients to “post-adjuvant” therapies.

Another key application of liquid biopsy is to identify therapeutic targets or mechanisms of resistance of metastatic cells in individual patients. While the analysis of ctDNA focuses on mutations relevant for cancer therapy (e.g., EGFR, KRAS or ESR1 mutations), CTCs offer a wide spectrum of analyses at the DNA, RNA and protein levels. Metastatic cells might have unique characteristics that can differ from the bulk of cancer cells in the primary tumor currently used for stratification of patients to systemic therapy. Moreover, monitoring of CTCs and ctDNA before, during and after systemic therapy (e.g., chemotherapy, hormonal therapy, antibody therapy) might provide unique information for the future clinical management of the individual cancer patient and might serve as surrogate marker for response to therapy. In the context of recent success in antibody-mediated blockade of immune checkpoint control molecules, expression of the PD-L1 on CTCs might be of interest as potential predictive marker. Moreover, the expression of androgen receptor variant 7 in CTCs may predict resistance to anti-androgen therapy in prostate cancer, while mutations in the estrogen receptor gene (ESR1) provides information on resistance to hormone therapy in breast cancer. Additional therapeutic targets detected on CTCs in cancer patients include the estrogen receptor and HER-2 oncogene. Single cell RNAseq analysis of CTCs may provide more comprehensive information on relevant pathways.

For functional analysis of CTCs, the development of *in vitro* and *in vivo* test systems has started, which might also serve as models for drug testing. In particular, the development of cell lines and xenografts derived from CTCs can provide novel insights into the biology of tumor cell dissemination and may be used to discover new pathways to target specifically metastatic cells.

Besides CTCs and ctDNA the analysis of circulating microRNAs, exosomes or tumor-educated platelets may provide complementary information as “liquid biopsy”. E.g., the integrin composition of exosomes seems to determine the organ site of metastatic niches and the RNA expression pattern of blood platelets reveals information

on tumors in cancer patients.

Sensitive methods have been also developed to capture disseminated tumor cells (DTCs) in the bone marrow in cancer patients, which provide new insights into the process of “cancer dormancy”. The nature of dormant breast cancer cells and the mechanisms leading to their outgrowth are poorly understood. Efforts to unravel the nature of cancer dormancy have been hampered by the lack of sensitive methods to detect dormant cells in cancer patients. The development of novel therapies designed to kill dormant residual tumor cells, or maintain them in a quiescent state, represents a highly attractive approach to prevent late recurrence. Such an approach, however, would require a far more detailed understanding of tumor dormancy and recurrence than exists today, as well as biomarkers to enable monitoring of this process and predict recurrence. Analysis of DTCs leads to the discovery of new molecules relevant to the biology of metastasis such as the putative metastasis-suppressor RAI2.

In conclusion, liquid biopsy analysis can be used to obtain new insights into metastasis biology, and as companion diagnostics to improve the stratification of therapies and to obtain insights into therapy-induced selection of cancer cells. Different approaches such as CTC or ctDNA analysis will provide complementary information. Technical and clinical assay validation is very important and can be achieved in international consortia such as the European IMI Cancer-ID network (www.cancer-id.eu).

Precision Medicine for Metastatic Breast Cancer Patients

Tuesday, 26th June - 09:40 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 190

Prof. Fabrice André [1]

1. *Gustave Roussy Institute*

Fabrice André, MD, PhD, received his MD in Grenoble in 2002, and a PhD in Biotechnology from Paris University in 2005. He is a past recipient of Young Investigator and Career Development awards from the American Society of Clinical Oncology (ASCO). He is currently Professor in the Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France. Professor André is conducting research in the field of biomarkers and personalised therapies. His research work focuses on biomarker discovery, development of targeted agents and implementation of personalised medicine. His team includes 70 people working on basic sciences, bioinformatics, biotechnologies and clinical research. Professor André is also leading phase I-III trials testing targeted agents in the field of breast cancer and large national trials testing implementation of high throughput technologies in the health care system. He has published more than 200 peer reviewed papers, including papers in the New England Journal of Medicine, Lancet, Nature Medicine, Science, Lancet Oncology and Journal of Clinical Oncology, either as main or co-author. Professor André is chairman of the biomarker group at UNICANCER (French cooperative group). He was a member of several scientific committees for international meetings, including SABCS, AAACR, ECCO, ESMO, and IMPAKT.

The epigenetics of colon cancer & the GCAT |Genomes for Life: a cohort of the genomes of Catalonia

Tuesday, 26th June - 10:45 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 24

Prof. Manuel Perucho [1], ***Dr. Sonia Forcales*** [2], ***Dr. Gabrijela Dumbovic*** [2], ***Dr. Sergio Alonso*** [2], ***Dr. Rafael De Cid*** [2]

1. *Program of Predictive and Personalized Medicine of Cancer (PMPPC), of the German Trias I Pujol Research Institute (IGTP). Barcelona.,* ***2.*** *PMPPC-IGTP. Barcelona.*

Global DNA hypomethylation increases with patient age and correlates with genomic damage in gastrointestinal cancers (Suzuki et al, *Cancer Cell*, 2006). This result led us to propose a "wear and tear" model linking aging and cancer by the unavoidable progressive erosion of genomic DNA methylation during aging. Two examples of "severe" DNA demethyation (higher than the average) did not comply with the "wear & tear" model.

Searching for biomarkers of multiple colon cancer (CC), we found that low levels of LINE-1 methylation (a surrogate marker of global levels of DNA methylation) correlated with the presence of synchronous CC and were predictive of high risk for developing metachronous tumors (Kamiyama et al., *Oncogene*, 2012). Thus, demethylation level can be used as prognostic biomarker for metachronous CC high risk. Among the patients with "severe" demethylation, those with multiple tumors were younger, supporting a role of genetic factors in multiple tumor risk.

In 22% of CC, a pericentromeric macrosatellite (SST1/NBL2), was found hypomethylated, of which 7% exhibited a "severe" hypomethylation (more than 10%) that co-occurred with *TP53* mutations in relatively younger patients (Samuelsson et al, *Epigenomes*, 2016). SST1/NBL2 is expressed as a novel long non-coding RNA that forms perinucleolar aggregates in a tight mirror image structure with SAM68 nuclear bodies (Dumbović et al, *NAR*, 2018), the function of which is under study.

The *Genomes for Life* (GCAT) is a long-term prospective cohort study ongoing at our institution that aims to explore the role of epidemiologic, environmental, genomic, and epigenomic factors in the development of cancer and other chronic diseases in Catalonia. The GCAT project has recruited near 20.000 participants at the end of 2017. Volunteers complete a detailed epidemiological questionnaire and undergo anthropometry measurements, and plasma, serum, and white blood cells are collected. The GCAT study has access to the Electronic Health Records (EHR) of the Catalan Public Health Care System. Participants will be followed at least 20 years after recruitment. Genomic and epigenomic analyses are being performed to investigate the association of epidemiologic, environmental and genetic risk factors with (multiple) CC and other cancers and chronic diseases.

Preparation of functional nanogels for tumor imaging and therapy

Tuesday, 26th June - 11:25 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 82

Prof. Xiangyang Shi [1], ***Ms. Wenjie Sun*** [1], ***Mr. Jianzhi Zhu*** [1], ***Ms. Yiwei Zhou*** [1], ***Dr. Chen Peng*** [2], ***Prof. Mingwu Shen*** [1]

1. *Donghua University,* ***2.*** *Tongji University*

Nanogels (NGs), physically or chemically cross-linked colloidal polymer networks, are hydrogels having a size in nanoscale and having combined properties of both nanoparticles (NPs) and bulk hydrogels. Their attractive properties afford their uses in a wide variety of biomedical fields. This talk will be focused on the recent progresses of the synthesis and functionalization of polymer NGs such as γ-polyglutamic acid (γ-PGA), alginate (AG), and poly(N□vinyl caprolactam) (PVCL) NGs for magnetic resonance (MR) imaging, computed tomography (CT) imaging, and photoacoustic (PA) imaging and photothermal therapy (PTT) of tumors performed in our group at Donghua University. In particular, γ-PGA and AG NGs formed via a double emulsion approach can be loaded with Fe_3O_4 nanoparticles (NPs), Mn_3O_4 NPs or Au NPs prestabilized by polyethylenimine (PEI) *via* an EDC-mediated crosslinking reaction for enhanced MR imaging or CT imaging of tumors. PVCL NGs formed via a precipitation polymerization method can be functionalized with DOTA(Gd) chelator for enhanced T_1-weighted MR imaging of tumors. In addition, we also prove that γ-PGA NGs can be used as a nanoreactor to bind aniline or pyrrole monomer for subsequent redox-mediated polymerization to generate polyaniline (PANI)- or polypyrrole (PPy)-loaded composite NGs that can be used as a unique platform for PA imaging-guided PTT of tumors. By further combination of radiotherapy, the developed PPy-loaded NGs can be used for enhanced PTT of tumors. Overall, through judicious design of functional NGs, various functional platforms may be developed for tumor imaging and therapy, which will bring broad interest for personalized medicinal applications.

Development and clinical translation of a handheld imaging device for 5-ALA-induced fluorescence guided breast conserving surgery

Tuesday, 26th June - 13:45 - Multi-Topics - Amphitheater - Oral - Abstract ID: 68

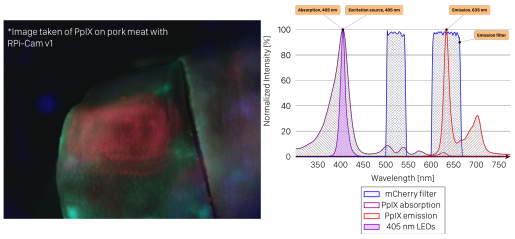
Mr. Christopher Gibson [1], ***Dr. Kathryn Ottolino-Perry*** [2], ***Dr. Alexandra Easson*** [2], ***Dr. Wey Leong*** [2], ***Dr. Susan Done*** [2], ***Dr. Ralph DaCosta*** [2]

1. *University of Toronto,* ***2.*** *University Health Network*

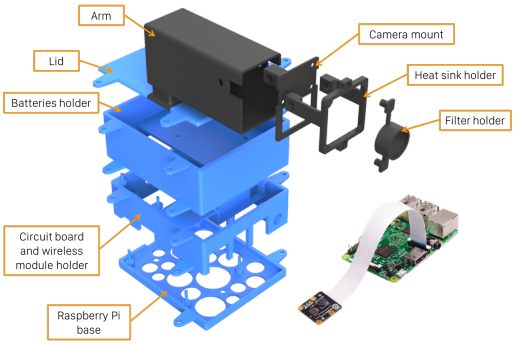
Twenty-three percent of patients who undergo breast conserving surgery (BCS) for early stage breast cancer require reoperation within 1y to remove residual tumour cells not detected in the initial surgery. Re-excisions increase discomfort, stress, adjuvant delay, medical costs, and local recurrence. The purpose of this project is to develop a new custom-designed handheld fluorescence imaging device that allows real-time visualization of residual breast tumour within the surgical cavity.We hypothesize that fluorescence-guided resection using this device with 5-aminolevulinic acid (contrast agent) will improve BCS resection completeness compared to the standard of care.

5-aminolevulinic acid (5-ALA) is an oral prodrug that promotes tumour-specific accumulation of protoporphyrin IX (PpIX), which primarily fluoresces (glows) bright red when excited with 405 nm (violet) light. We have previously demonstrated a proof-of-concept to image breast tumour margins intraoperatively based on 5-ALA-induced PpIX fluorescence in resected tissues (clinicaltrials.gov ID NCT01837225). Clinical user feedback from this ongoing trial has informed the design of an optimized fluorescence imaging prototype device that will be tested in tissue phantoms painted with PpIX. Following initial validation of the new device, we will test our hypothesis in a recently funded Phase III Pan-Canadian multicentre randomized clinical trial (“The Canadian FIGHT Breast Cancer Surgical Trial”; PI: R. DaCosta).

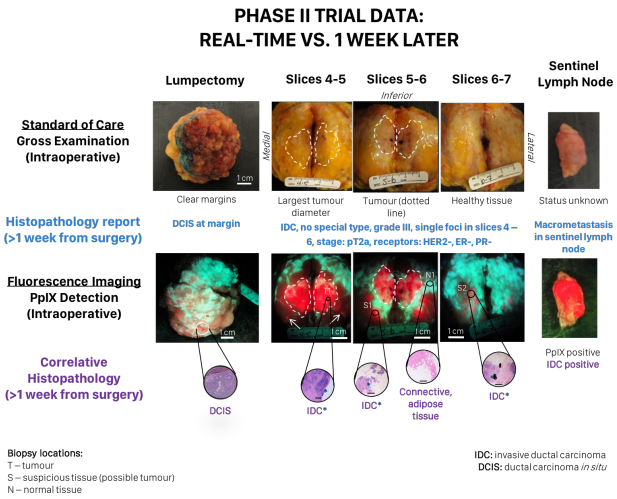
We built a new proof-of-concept imaging device (RPi-Cam) which captures and streams fluorescence images wirelessly to a computer in real-time. We have successfully demonstrated detection of PpIX on pork tissue with RPi-Cam. Additionally, RPi-Cam includes white light illumination for anatomic colocalization of PpIX. Next steps include preparing RPi-Cam for trial readiness by miniaturizing into a clinically-informed housing design. In its early stages, RPi-Cam provides a number of benefits over competing technologies. We anticipate the results of this study will elucidate the clinical applicability of intraoperative fluorescence image guidance for BCS.



Rpi-cam imaging.png



Rpi-cam design.png



Ex vivo breast tumour fluorescence imaging.png

Genomic Association Study of Warfarin in Caribbean Hispanics.

Tuesday, 26th June - 14:05 - Multi-Topics - Amphitheater - Oral - Abstract ID: 49

Dr. Karla Claudio-Campos [1], Ms. Aurora Labastida [2], Dr. Alga S Ramos [1], Dr. Andrea Gaedigk [3], Mrs. Jessicca Y Renta [1], Ms. Dariana Padilla [1], Dr. Stuart Scott [4], Dr. Gualberto Ruano [5], Dr. Carmen Cadilla [1], Dr. Duconge Jorge [1]

1. *University of Puerto Rico Medical Sciences Campus,* ***2.*** *Thermofisher Scientific,* ***3.*** *Children's Mercy Hospital and Clinics, Kansas City,* ***4.*** *Icahn School of Medicine, Mount Sinai,* ***5.*** *Hartford Hospital*

INTRODUCTION: Despite the advent of the new direct oral anticoagulants, warfarin continues to be a mainstay therapy in thromboembolic disorders. Warfarin dosing requirements are highly variable and it may lead to serious adverse events. Existing genotype-driven algorithms account for □50% of this variance, but they do not perform as well in populations other than Caucasians because some ethno-specific alleles are overlooked. The impact of pharmacogenomics on dose requirements for Hispanics is unknown due to their underrepresentation in clinical trials. This study was aimed to identify genetic polymorphisms that can explain variability in warfarin dosing among Caribbean Hispanics. METHODS: A case-control pharmacogenetic association study was conducted in 275 Puerto Rican patients on warfarin, using the Extreme Discordant Phenotype approach. Next-Generation Sequencing of candidate genes *CYP2C9* and *VKORC1* and genotyping by DMET®-Plus Array were performed. RESULTS: An admixture-adjusted pharmacogenetic model that explained more than two-thirds of observed variance in stable warfarin dose in Caribbean Hispanics was developed (**Fig.1**). *CYP4F2**3 and *NQO1**2 variants were independently associated with a 17 and 10% increase of the dose per allele, respectively. On the other hand, the admixture index decreases the dose by 7%. The African-related rare *CYP2C9**8 allele explained 31% decrease of the dose. The genomic diversity of Puerto Ricans is highlighted by the presence of 11 major *CYP2C9* haplotypes (**Fig.2**). The *CYP2C9* rs2860905 variant showed stronger association with warfarin sensitivity than common *CYP2C9**2 and *3 alleles (**Fig.3**). Incorporation of rs2860905 in a model that also includes additional genetics (*VKORC1*-1639G>A; *CYP2C9*rs1856908; *ABCB1*c.IVS9-44A>G; *CES2*c.269-965A>G) and non-genetic factors showed better prediction of warfarin dose requirements. The genetic background of participants showed a tri-hybrid admixture pattern. DISCUSSION: Although our findings need further replication, our study contributes to the field by identifying novel genetic variants that increase predictability of warfarin dosing among Caribbean Hispanics. We described variants in *CYP2C9* (e.g., rs2860905) and other pharmacogenes (e.g., *NQO1*, *CES2*) that were found for the first-time ever to be significantly associated with warfarin dose requirements in a cohort of Caribbean Hispanics. We concluded that admixture and ethno-specific alleles are both clinically relevant predictors for algorithmically computed warfarin doses in Caribbean Hispanics.

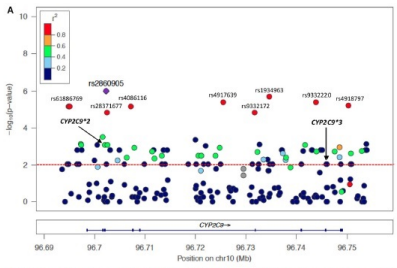


Figure 3. Single nucleotide variants (SNVs) at *CYP2C9* associated with warfarin sensitivity, identified with NGS. P-values correspond to case-control association test performed in patients of the study cohort but colored codes represent correlation of SNVs with rs2860905 among Hispanics from 1,000 Genomes (Puerto Ricans, Colombians, Mexican Americans and Peruvians).

Fig3 pemed 2018 duconge abstract.jpg

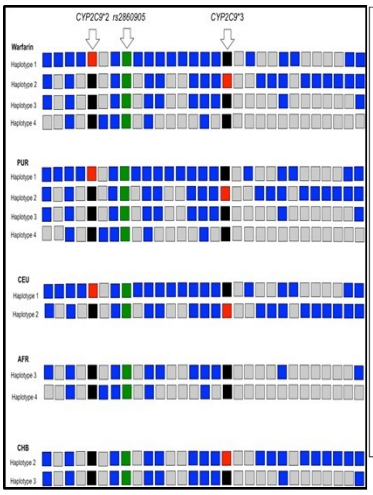


Figure 2. Representation of the most frequent haplotypes found within the region spanning *CYP2C9* (chr10: 96694843 to 96750251) across patients in warfarin and parental populations from the 1000 Genomes Project (Caucasians, Africans and Asians). Each block represents a position within the haplotype (haplotypes 1-4, H1-4). Blue blocks indicate the presence of the variant allele for each of the positions while gray blocks indicate the presence of the wild-type allele. The green block is the presence of the variant rs2860905. Red blocks represent the variants *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910). The data was obtained from the 1000 Genomes Project Phase 3 with phased genotypes.

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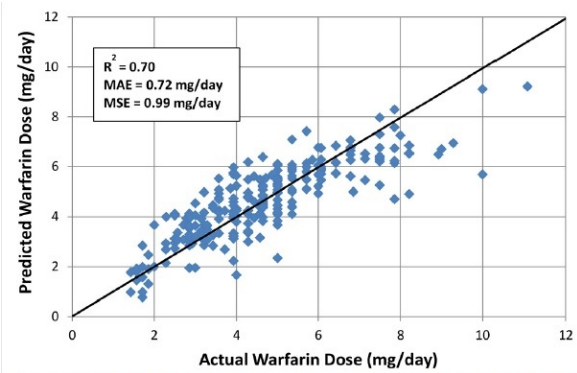


Figure 1. Pharmacogenetic-guided algorithm to predict warfarin dose requirements in Caribbean Hispanic patients, developed by using a multiple regression analysis. The solid line depicts perfect prediction of the model. The stabilization dose refers to the dose given after three consecutive INRs values within the range (2–3 for most of the indications). The R^2 value is adjusted. MAE and MSE stand for mean absolute error and mean standard error respectively.

Fig1 pemed 2018 duconge abstract.jpg

Defining new strategies for therapy in PRKAG2 mutations and hypertrophic cardiomyopathy: implications for personalised medicine in inherited cardiac disorders

Tuesday, 26th June - 14:25 - Multi-Topics - Amphitheater - Oral - Abstract ID: 144

Dr. Rameen Shakur [1], ***Mr. Juned Kadiwala*** [1], ***Dr. Robert Lowe*** [2]

1. *University of Cambridge,* ***2.*** *universtity of london, QMUL*

Introduction

PRKAG2 cardiomyopathies are autosomal dominant inherited heart muscle diseases often characterized by left ventricular hypertrophy (LVH), progressive conducting abnormalities and ventricular pre-excitation Wolff-Parkinson-White [WPW] syndrome. However, AMPK mutations especially in the gamma 2 subunit are accompanied with chronotropic incompetence, glycogen accumulation and advanced heart blocks leading to premature pacemaker implantation. Therapeutic options to better control the arrhythmic potential and the underlying biological sequelae from such mutations remain an enigma. We investigate the application and development of a novel drug discovery platform to elucidate the mechanism of this disorder and a potential therapy which was taken into the clinic as an example of a bench to bedside protocol.

Methods

Human Induced Pluripotent Stem cells (hIPSc) were derived using a novel protocol from urine and subsequently differentiated to cardiomyocytes using a chemically defined protocol. This was used as the modelling tool for this study. An integrated approach utilising transcriptomic and proteomic data as a platform was used to define candidate proteins implicated within the mutant lines. Isogenetic lines were also produced using a modified Crispr-Cas9 system. In addition, homozygote gene correction of underlying mutant lines was also undertaken with review of potential off targets and karyotype status.

Results

Carvedilol was the only drug that was defined as having a novel mechanism of action on AMPK and on AMPK mutations directly using our platform, this was not a class effect.

One year follow up data of the patient showed statistically significant reduction in atrial (P=0.01) and ventricular (P=0.01) arrhythmia burden. Furthermore, there was a substantive reduction in BNP and a general increase in LVEF overall.

Discussion

This study represents the first of its kind to clinically verify drugs specific for therapy within the spectra of personalized medicine. It is also the first example of compound mutation correction in human cardiomyocytes as a means to better elucidate mechanism of action from mutation to clinical output. This real world platform shows a novel proof of concept means to provide potential candidates for a more tailored personalized therapy in cases of inherited cardiac disorders whereby therapy remains an overwhelming goal.

Measurements of Heterotypic Associations Between Cluster of Differentiation CD74 and CD44 in Human Breast Cancer-Derived Cells

Tuesday, 26th June - 15:15 - Personalized therapies - Amphitheater - Oral - Abstract ID: 8

Dr. Hussain Alssadh [1], *Dr. Patrick Spencer* [1], *Dr. Waleed Al abdulmonem* [2], *Dr. Rana Alghamdi* [1], *Dr. Inamul Hassan* [3], *Dr. Jose M. Miranda-sayago* [1], *Prof. Neslon Fernández* [1]

1. *University of Essex*, **2.** *Qassim University*, **3.** *Bharathidasan University*

Interactions between pairs of membrane-bound receptors can enhance tumour development with implications for targeted therapies for cancer. Here we demonstrate clear heterotypic interaction between CD74 and CD44, which might act in synergy and hence contribute to breast cancer progression. CD74, a type II transmembrane glycoprotein, is a chaperone for MHC class II biosynthesis and a receptor for the MIF. CD44 is the receptor for hyaluronic acid and is a Type I transmembrane protein. Interactions between CD74, MIF and the intra-cytoplasmic domain of CD44 result in activation of ERK1/2 pathway, leading to increased cell proliferation and decreased apoptosis. The level of CD44 in the breast tumor cell lines CAMA-1, MDA-MB-231, MDA-MB-435 and the immortalized normal luminal cell line 226LDM was higher than that of CD74. It was also observed that CD74 and CD44 exhibit significant variation in expression levels across the cells. CD74 and CD44 were observed to accumulate in cytoplasmic compartments, suggesting they associate with each other to facilitate tumour growth and metastasis. Use of a novel and validated colocalisation and image processing approach, coupled with co-immunoprecipitation, confirmed that CD74 and CD44 physically interact, suggesting a possible role in breast tumour growth. This is the first time that CD74 and CD44 colocalization has been quantified in breast cancer cells using a non-invasive and validated bioimaging procedure. Measuring the co-expression levels of CD74 and CD44 could potentially be used as a 'biomarker signature' to monitor different stages of breast cancer.

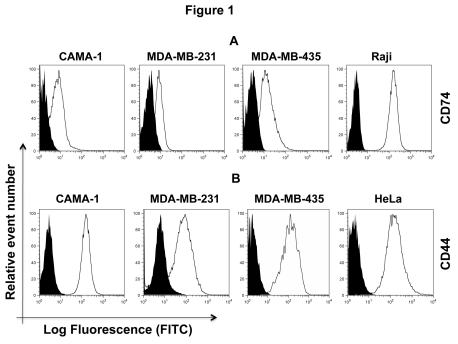


Fig 1.jpg

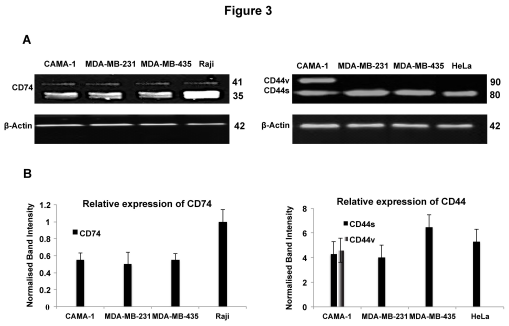
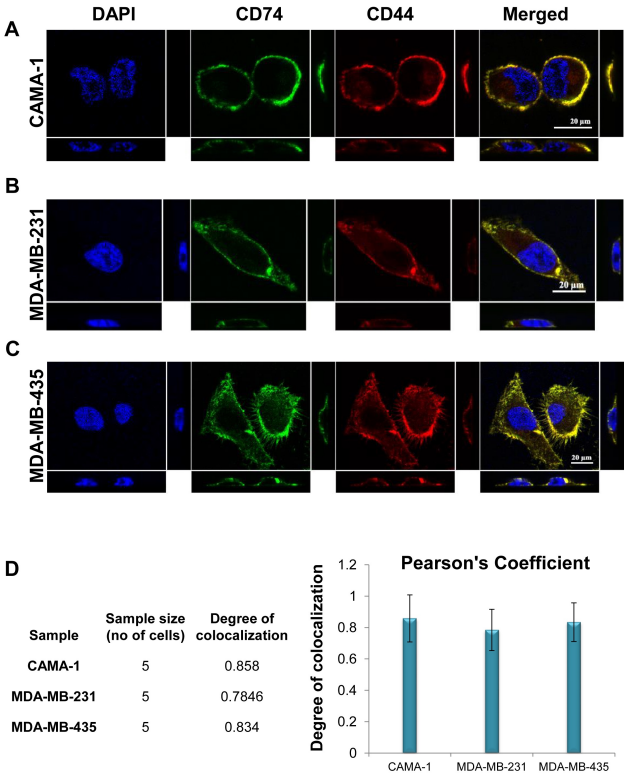


Fig 3.jpg

Figure 5



D

Sample	Sample size (no of cells)	Degree of colocalization
CAMA-1	5	0.858
MDA-MB-231	5	0.7846
MDA-MB-435	5	0.834

Fig 5.jpg

Precision Medicine and immunomodulatory therapy for Stevens Johnson Syndrome/Toxic Epidermal Necrolysis.

Tuesday, 26th June - 15:35 - Personalized therapies - Amphitheater - Oral - Abstract ID: 139

Prof. Omer Iqbal [1]

1. *Loyola University Medical Center*

Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) is a rare but fatal immune-mediated Severe Cutaneous Adverse Reaction (SCAR) which is often drug-induced frequently involving the eyes leading to corneal blindness. The pathophysiology is not completely understood and despite symptomatic treatment involving a multidisciplinary approach there is significant morbidity and mortality. The survivors most often have long-term ocular sequelae. Given the natural history of SJS/TEN and involvement of various Human Leucocyte Antigen (HLA) genes affecting different ethnic groups globally, conducting a multi-centric clinical trial with required optimum number of subjects could be quite a challenge. Patient registries provide useful data but may be difficult or impossible to control for confounding variables and bias. However, lack of adequate patient registries as in SJS/TEN may pose additional problems. Given that this condition is drug-induced with more than 200 drugs known to be serious culprits, the existing and future drug pipelines are warranted to undergo cheminformatics-aided pharmacovigilance in order to control the incidence of SJS/TEN. Although HLA genes are associated with this condition together with specific culprit drugs, but identification of how the HLA genes interact with the drug in the host system is of paramount importance in disease prevention, and earlier diagnosis in order to have a strategic multidisciplinary approach in its treatment. With the advent of Precision Medicine, newer study designs pertaining to randomized clinical trials for rare diseases have to be established and technological advances such as exome sequencing used in order to achieve tangible clinical outcomes. It is crucial to carefully map the genomic landscape of rare diseases like SJS/TEN in order to assess the response to combination immunomodulatory therapy. Although some of the currently available immune check point inhibitors may trigger SJS/TEN as adverse effects, a careful designing of immunomodulatory drugs is warranted. This presentation will provide a unique blend of discussions on the challenges of clinical trials on rare diseases in general and SJS/TEN in particular combined with the clinical manifestations of this rare condition and the potential role of selective immunomodulatory therapy.

Applications of artificial intelligence in precision medicine

Tuesday, 26th June - 15:55 - Personalized therapies - Amphitheater - Oral - Abstract ID: 129

Mr. Michal Madera [1], ***Prof. Jacek Kluska*** [1]

1. *Rzeszow University of Technology*

Precision medicine (PM) can be understood as an approach to the prevention and treatment of diseases through such development of diagnostics and therapy that takes into account information about particular genes and integrates clinical and molecular information, as well as the patient's environment and lifestyle. Advances in biological and medical technologies provide us with enormous amounts of data in the form of images, texts, numbers or multimedia messages. Genome sequencing, advanced biotechnology or various health sensors used by patients, with handheld devices, including smartphones, watches, etc., produce a huge amount of data. Learning from these data makes it easier to understand human health and diseases. Big data is so huge and complex that traditional data processing software is not enough to deal with it. Data of this type must be appropriately captured, stored, analyzed, searched, shared, transmitted, visualized and updated. Serious problems concern the privacy of medical information and the source of such data. In our times, the challenge is the problem of processing such data, which are usually noisy and often are in the form of streams coming in real-time. Machine learning techniques (ML) help in solving diagnostic and prognostic problems in various fields of medicine. ML is used to analyze the significance of clinical parameters and their combinations for the prognosis, e.g. prediction of disease progression, extraction of medical knowledge. All this in combination with individual clinical and molecular information, the environment and lifestyle factors, are a contribution to precision medicine.

The aim of this paper is to provide a review of recent machine learning techniques and some of the state-of-the-art applications used in precision medicine. We pay attention to why and where big data are and which methods have succeeded. We show examples of applications of machine learning, including classification of medical images, analysis of genomic sequences, as well as classification and prediction of protein structure. At the end, we present our point of view regarding future applications of computational intelligence in precision medicine.

CDA status predicts life-threatening toxicities in AML patients treated with cytarabine

Tuesday, 26th June - 16:15 - Personalized therapies - Amphitheater - Oral - Abstract ID: 38

Dr. raphaelle fanciullino [1], ***Dr. Laure Flahault*** [1], ***Mrs. Melanie Donnette*** [2], ***Dr. Diane-charlotte Imbs*** [2], ***Dr. Vadim Ivanov*** [1], ***Dr. Geoffroy Venton*** [1], ***Dr. Ciccolini Joseph*** [2], ***Prof. L'houcine Ouafik*** [1], ***Prof. Bruno Lacarelle*** [3], ***Prof. Regis Costello*** [1]

1. *Assistance Publique Hôpitaux de Marseille,* ***2.*** *Aix Marseille Univ,* ***3.*** *laboratory of pharmacokinetics - La Timone*

Induction phase with Cytarabine (Ara-C) is a mainstay to treat accute myeloid leukemia (AML) and severe/lethal toxicities are frequent. Ara-C is metabolized in the liver by an exclusive enzymatic step by cytidine deaminase (CDA). CDA is a ubiquitous enzyme coded by a highly polymorphic gene, with subsequent phenotypes ranging from poor metabolizer (PM) to ultra metabolizer (UM) patients. To what extent CDA phenotype could help predict clinical outcome in Ara-C-treated patients remains to be established. In this clinical observational study we studied whether CDA deficiency could be at the origin of severe/lethal toxicities in AML patients undergoing induction phase with Ara-C. CDA activity and 79A>C *CDA* genetic polymorphism was evaluated in 58 adult patients (25F, 33M, mean age 63 ±15 years). All patients were treated following current standard care by Ara-C-containing regimen (i.e., 7+3 protocol) and monitored for toxicity and response. Mean CDA activity was 3.14 ± 3 U/mg. The incidence of CDA deficiency was much higher in AML patients (41%) than what we previously observed in patients with solid tumors (i.e., 5-7%). No relationship was found between CDA phenotype and genotype. A total of 20 patients (43%) displayed severe toxicities upon administration, including 3 toxic-deaths (5%). ROC analysis identified a cut-off value in CDA ≤ 2 U/mg associated with increased risk of severe/lethal toxicities with 74% sensitivity and 65% specificity. Among the 20 patients with severe toxicities, 14 (72 %) were categorized as PM. Importantly, patients who experienced lethal toxicities were all profoundly PM patients. CR was achieved in 35 patients (60%), CRi in 4 patients (7%) whereas 16 patients (27%) had Progressive Disease. No relationship was evidenced between CDA status and response, however PM patients tended to have longer PFS (278 vs. 517 days) and OS (570 days vs. not reached) than EM patients. Overall this proof-of-concept study suggests that CDA could be a relevant marker for predicting clinical outcome in patients treated with Ara-C. This marker could be used next as a covariate to customize Ara-C dosing in AML patients so as to reduce the risk of severe or lethal toxicities.

Identifying Hyperphoria as a Leading Cause of Migraines and Linking Similarities to Seizures with Binocular Exams and Prisms

Tuesday, 26th June - 15:15 - Emerging opportunities in personalized medicine - 217 - Oral - Abstract ID: 41

Dr. David Chang [1]

1. *David LH Chang, O.D.*

The presenter will share his precise predictive hyperphoria values for migraines and its link to seizures. He will present two migraine cases to highlight what is common across all his migraine patients. These two cases will reveal the etiology, the cure and the best treatment for migraines. The treatment methodology is based on strain reduction through proper balanced refraction and phoria reduction. The presenter will share what was learned from these cases and how it can be applied to future cases as well as to seizure cases.

An AI Enable Digital Physical Exam for the future of Precision Medicine

Tuesday, 26th June - 15:35 - Emerging opportunities in personalized medicine - 217 - Oral - Abstract ID: 57

Mr. Mark Punyanitya [1], ***Dr. Girish Srinivasan*** [1], ***Mr. Zachary Rapp*** [1]

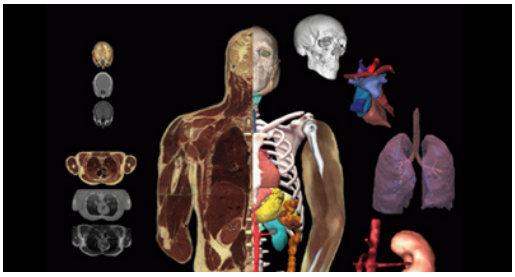
1. *PhenoMx, Inc.*

The time has come where technology is available to create a Digital Physical Examination of the whole body, based on non-invasive imaging.

With increasing focus on genomic, metabolomic, and molecular quantification of the human body for use in precision medicine, the development of diagnostics, therapeutics, and monitoring of disease progression/treatment takes on a greater role for more effective outcomes. The majority of advances have not included the phenotype, or observable characteristics of an individual resulting from the interaction of its genotype with the environment.

Biomarkers provide researchers and clinicians with useful measurements that allow for earlier diagnosis before a patient begins to show signs of symptoms, and also quantitatively shows that a treatment is performing effectively. Non-invasive imaging technology is now available to measure the vital organs & major tissue systems of the whole body within one complete exam.

This session will provide insight via a Case Study into the first International Precision Medicine Center to incorporate the Digital Physical Examination as an Imaging Phenotype, alongside the existing battery of advanced testing.



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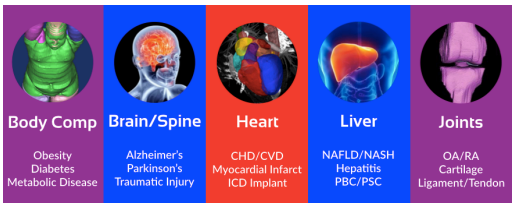

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Detecting pre-cancers by liquid biopsy: The proof-of-principle and dilemma.

Tuesday, 26th June - 15:55 - Emerging opportunities in personalized medicine - 217 - Oral - Abstract ID: 50

. John Martignetti [1], ***Mr. Deep Pandya*** [2], ***Dr. Nimesh Nagarsheth*** [1], ***Dr. Ying Chen*** [1], ***Dr. Olga Camacho-vanegas*** [1], ***Dr. Robert Sebra*** [1], ***Dr. Boris Reva*** [1], ***Dr. Peter Dottino*** [1]

1. *Icahn School of Medicine, Mount Sinai,* ***2.*** *Western Connecticut Health Network*

In contrast to the previously successful TCGA goals of cataloguing the genomic landscape of advanced disease, we currently lack understanding of the multi-omics landscape and ordering of the sequence of genetic events and immunologic features which lead to cancer. This limited understanding of pre-cancer biology ultimately becomes an insurmountable roadblock for early cancer detection and prevention: as cancer-driver mutations are now being reported with increasing frequency in aging but apparently normal tissues, we cannot distinguish between a benign molecular lesion conferring a proliferative growth advantage and a clonal population committed to malignancy. This results in a clinically-relevant dilemma wherein the technology to detect mutations is available but the pre-cancer knowledge gap means mutation detection is not actionable.

Endometrial cancer is the most common gynecologic malignancy in industrialized countries and, given the rise in obesity, both its incidence and associated mortality are increasing. There is no screening test for this cancer. Recently, NGS technologies have been coupled to an almost abandoned technique first introduced sixty years ago, the uterine lavage, to detect endometrial and ovarian cancers. We demonstrated the ability to sequence DNA isolated from uterine lavage fluid to detect even microscopic cancers.

We now report the clinical and molecular follow-up of an originally asymptomatic 67yo female with histology-proven benign endometrium with no evidence of hyperplasia or cancer but with lavage-detected, oncogenic PTEN driver mutations who returns one year later with postmenopausal bleeding and a single microscopic focus of endometrial cancer. The same PTEN mutations detected in lavage were also present in her tumor. We calculated that the shared mutations across samples were not likely to occur by chance alone ($p < 3x10^{-7}$).

Using an integrated liquid biopsy-based and cancer-targeted sampling approach, we have established a benchmark for earliest endometrial cancer detection. This illustrative case provides the first demonstration that future, tumor-specific mutations can be identified in an asymptomatic individual without clinical or pathologic evidence of cancer. The results are discussed in the context of follow-up of other patients and molecular profiles, the implications for precision medicine and the urgent need for understanding pre-cancer biology.

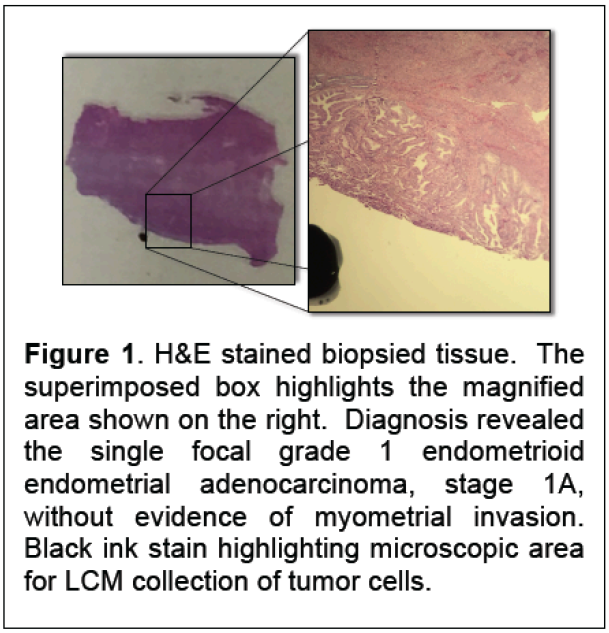


Figure 1. H&E stained biopsied tissue. The superimposed box highlights the magnified area shown on the right. Diagnosis revealed the single focal grade 1 endometrioid endometrial adenocarcinoma, stage 1A, without evidence of myometrial invasion. Black ink stain highlighting microscopic area for LCM collection of tumor cells.

Screen shot 2018-01-15 at 6.02.13 pm.png

New Key Questions and Tests to Precisely Identify Asthenopia Problems for Physicians, Parents and Patients

Tuesday, 26th June - 16:15 - Emerging opportunities in personalized medicine - 217 - Oral - Abstract ID: 15

Dr. David Chang [1]

1. *David LH Chang, O.D.*

There is growing evidence that common neurological symptoms and complaints, such as headaches, migraines, ADHD, dyslexia, seizures and autism may all originate from asthenopia or eye strains. The presenter will share his experience, analysis and insights for each of these diseases.

He will present new key questions and tests that he has designed and successfully used in his practice. These questions and tests can be used by physicians or eye and neurologic specialists to precisely diagnose asthenopia. The recommended tests will also reveal the expected results from a more thorough binocular eye exam.

These simple but powerful recommendations will ensure the right diagnosis and treatment, avoid excessive referrals, testing and healthcare costs, for patients and society while improving the patients' overall well-being and quality of life.

Fluorescence-guided tumor surgery using a new RGD-based probe

Tuesday, 26th June - 17:00 - Biomarkers and diagnostics, imaging, biochip/microarray technologies - Amphitheater - Oral - Abstract ID: 122

Dr. Alessia Cordaro [1], ***Dr. Chiara Brioschi*** [2], ***Dr. Federica Chianale*** [2], ***Dr. Luigi Miragoli*** [2], ***Dr. Paolo Oliva*** [2], ***Dr. Giovanni Valbusa*** [3], ***Dr. Francesco Blasi*** [2], ***Dr. Federico Maisano*** [2], ***Prof. Enzo Terreno*** [1]

1. *University of Turin,* ***2.*** *Bracco Imaging SpA,* ***3.*** *EPHORAN - Multi Imaging Solutions*

Introduction –Despite many improvements in the treatment of cancer, surgery remains the most important curative option for solid tumors. Fluorescence-guided surgery is a promising strategy to improve surgical resection, with the aim of reducing local recurrences and increasing survival rate.

Integrins are an attractive biomarker for targeted imaging-guided surgery. $\alpha_v\beta_3$Integrin is usually expressed at undetectable levels in most adult epithelia, but it is highly up-regulated in tumors and correlates positively with disease progression.

To visualize $\alpha_v\beta_3$integrin expression in real time during tumor resection, a new cyclic RGD-based peptidomimetic was conjugated with cyanine 5.5, a near-infrared (NIR) fluorophore. The *in vitro*, *in vivo* and *ex vivo*characterization of this conjugate, coded B26100, is presented here, to show its affinity for the target receptor and its capability to identify tumor mass and margins.

Methods -ELISA and Maximum Absorbance Shift techniques were used to measure the affinity of the probe for $\alpha_v\beta_3$integrin and serum albumin respectively. Flow cytometry and cell assays were used to assess the interaction of the probe with tumor cells. Nude mice bearing tumors from U87-MG human glioblastoma and A431 human epidermoid carcinoma cells were chosen for *in vivo*optical imaging experiments, to evaluate the efficacy and biodistribution of the probe. The ability of B26100 in identifying tumor masses during surgery was tested on rat MAT-Ly-Lu tumor, an orthotopic prostatic model.

Results –B26100 exhibited high affinity to isolated $\alpha_v\beta_3$ integrin and moderate binding to serum albumin. The molecule was able to enter $\alpha_v\beta_3$-expressing cells, mainly by integrin-mediated internalization mechanism. *In vivo* optical imaging showed that the probe allows to visualize tumor masses, with low retention in healthy tissues and preferential accumulation in tumors that overexpress the target. During surgery, the molecule enabled the discrimination between MAT-Ly-Lu tumor and the surrounding healthy prostate, facilitating the complete removal of pathological tissue, while sparing the healthy one.

Discussion – B26100, a new fluorescent RGD-based molecule, can be used for sensitive outlining of tumor lesions *in vivo*. It is a promising optical imaging probe for fluorescence-guided surgery, identifying specifically tumor margins and enabling the precise tumor mass removal.

Methylation status of tumor suppressor genes in glioblastomas: evidence of survival correlation

Tuesday, 26th June - 17:20 - Biomarkers and diagnostics, imaging, biochip/microarray technologies - Amphitheater - Oral - Abstract ID: 152

Dr. Saoussen Trabelsi [1], Ms. Ameni Touati [1], Ms. Nesrine Ben Salah [1], Ms. Maroua Mastouri [1], Prof. Nadia Mama [2], Prof. Mohamed Ladib [3], Prof. Slim Ben Ahmed [4], Prof. Noureddine Bouaouina [5], Prof. Moncef Mokni [6], Prof. Hedi Krifa [3], Prof. Ali Saad [1], Prof. Kalthoum Tlili [2], Prof. Chris Jones [7], Prof. Dorra H'mida [1]

1. Farhat HACHED university hospital . department of cytogenetics, molecular genetics and reproductive biology, 2. Sahloul university hospital . department of imagery, 3. Sahloul university hospital . department of neurosurgery, 4. Farhat HACHED university hospital . department of oncology, 5. Farhat HACHED university hospital . department of radiotherapy, 6. Farhat HACHED university hospital . department of cytopthology, 7. Divisions of Molecular Pathology and Cancer Therapeutics.The Institute of Cancer Research. London.

Introduction: Glioblastomas (GB) are heterogeneous group of tumors with poor patient's outcome. Recent discoveries reported the evidence that both genetic and epigenetic mechanisms drive GB malignancy. A major challenge becomes to identify molecular markers that could influence patient's outcomes. Genetic investigations amply contribute to sub-classify GB according their prognostic. Epigenetic analysis could thus disclose further potential biomarkers.

Methods: We applied Methylation Specific-MLPA technique to investigate the association between tumor suppressor genes methylation with overall survival (OS) in retrospectively collected clinical and molecular data of 50 GB.

Results: OS was significantly longer for patients with tumors harboring hypo-methylated tumor suppressor gene profile (*Kaplan Meier survival test*p=0.002). Distinctive methylated gene panels that confer poor outcome were associated with GB molecular subtypes that exhibited either EGFR amplification or IDH1 R132H mutation. Moreover, TP53, TP73, BRCA1, BRCA2 and ATM methylation were independently associated with poor outcome.

Discussion: Our study demonstrates that tumor suppressor genes methylation status significantly affects patients' overall survival afflicted with GB. Furthermore, epigenetic biomarkers were differentially associated to molecular GB subtypes.

A novel predictor for stratifying pancreatic cancer patients to DNA damage checkpoint inhibitors

Tuesday, 26th June - 17:40 - Biomarkers and diagnostics, imaging, biochip/microarray technologies - Amphitheater - Oral - Abstract ID: 85

Dr. Dannel Yeo [1], Dr. Robert Jorissen [2], Prof. Mehrdad Nikfarjam [1], Dr. Petranel Ferrao [1]

1. *University of Melbourne,* ***2.*** *The Walter and Eliza Hall Institute of Medical Research*

Introduction

CHK1 is a key DNA damage checkpoint kinase involved in cell cycle arrest and DNA repair. CHK1 inhibitors (CHK1i) were originally developed as chemo-potentiators in cancers with p53 mutations. Several CHK1i have been in clinical evaluation recently. We have shown that cancers with oncogene-induced replicative stress are particularly susceptible to CHK1 inhibition. However, advancement of CHKi as effective therapies in the clinic requires patient stratification using predictive biomarkers of response. A novel predictor of CHK1i response identified using *in vitro* pharmaco-trancriptomic analysis was assessed as a potential biomarker for identifying pancreatic cancers (PaCa) responsive to combination treatment with Gemcitabine (Gem) and CHK1i.

Methods

A PaCa cell line panel was assessed for response to Gem and CHK1i currently in clinical evaluation using dose response assays. Correlation analysis of Gem or CHKi IC_{50} with expression of our biomarker, CHK1 activation, DNA damage and DNA damage response (DDR) signalling was conducted. Combination treatments at varying doses were assessed for synergy using the excess over Bliss Independence, and the effects of pre-treatment on drug synergy was assessed to determine the influence of drug scheduling.

Results

High expression of the biomarker correlated with higher relative IC_{50} to Gem and CHK1i drug treatment. Combination treatment of Gem+CHK1i was synergistic in the cell lines resistant to Gem, suggesting effective chemosensitisation in PaCa with high expression of the biomarker. Pre-treatment of PaCa lines was able to influence the level of synergy of Gem+CHK1i combination, suggesting that scheduling of treatment could influence treatment responses.

Discussion We predict that our novel biomarker will be highly beneficial in identifying patients with Gem-resistant PaCa who may benefit from combination treatment with CHKi. We also propose that drug scheduling could be utilised to enhance the efficacy of Gem+CHK1i combination treatment in this patient subgroup.

This project is made possible by an Avner Pancreatic Cancer Foundation grant www.avnersfoundation.org.au

Epigenetics for Precision Health and Performance

Tuesday, 26th June - 17:00 - Epigenetics Workshops - 217 - Workshop - Abstract ID: 142

Dr. Mickra Hamilton [1]

1. *Apeiron Center for Human Potential*

A precision, whole systems genomic approach to thriving health and well-being has enormous clinical applications in the emerging field of environmental epigenetics. We can now evaluate all aspects of an individual's life, their medical and family history, occupation, lifestyle, home and work environments, human systems diagnostics and genetics. Additionally, we have real time markers from sensor and movie data to design lifestyle interventions to optimize and enhance gene expression. This new precision offers high specificity on health, tracks how individual choices affect health now and how that translates to the future. It also provides new insights about how we are interacting with our environment in real time and in real detail. The interplay of our genes and our experiences, of nature and how it interacts with nurture, has now moved from the mysterious to the knowable.

The Science of Epigenetics assists us to create precise optimization strategies by taking the reigns of gene expression to adapt and thrive under modern environmental pressures. Every decision we make contributes to this process in some way. The food we eat, the quality of sleep that we experience, the cars we drive, the products we clean with and put on our skin, the thoughts we think, the levels of stress we carry and the chemicals and medications we dump into our water supply, all have an effect.

This discussion will detail the evidence-based use of precision epigenetics and genomics as strategies to mitigate the effects of environmental toxins in the human system. Additionally, I will discuss actionable lifestyle modifications and human systems support processes to fine tune human health as we interact with our environment. based use of precision epigenetics and genomics strategies to mitigate the effects of environmental toxins in the human system. Additionally, we will discuss action able lifestyle modifications and system support processes to fine tune and enhance our human experience as we interact with our environment.

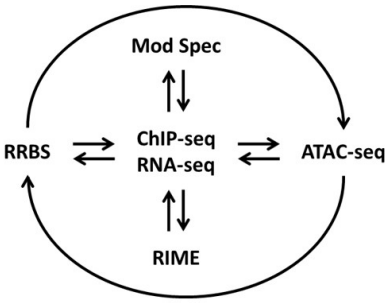
A Multi-Omics approach to define the epigenetic profile of your model system

Tuesday, 26th June - 18:00 - Epigenetics Workshops - 217 - Workshop - Abstract ID: 101

Dr. Sarantis Chlamydas [1]

1. *Active Motif*

Epigenetic profiling is critical for understanding the underlying mechanisms involved in cell fate decisions, cellular response to treatment and disease. Unfortunately, no single assay can provide a comprehensive view of the epigenetic state of your cells of interest. Here, we present different services offered by Active Motif that, when performed in union, can provide a comprehensive understanding of epigenetic determinants that are involved in your model system and be used for tumor profiling, biomarker and drug discovery research. Active Motif's comprehensive service offering includes: 1) **ATAC-seq** (Assay for Transposase-Accessible Chromatin using sequencing), which interrogates chromatin accessibility changes in your cells or tissues of interest; 2) **Mod Spec™**, which quantifies histone post-translational modifications by mass spectrometry, making it possible to measure global changes of greater than 80 different histone modification states in a single assay; 3) **ChIP-Seq** (Chromatin Immunoprecipation Sequencing) experiment, an essential tool to study Chromatin and Transciption Biology using tumors cells or tissues as well as FFPE samples. Using specific antibodies, we can follow the binding pattern of chromatin proteins, elucidating their function and their correlation with different gene regulation pathways. 4) **RRBS** (Reduced Representation Bisulfite Sequencing) which provides single base-pair resolution methylation status at over 75% of CpG islands and over 50% of promoters; 5) **RIME** (Rapid Immunoprecipitation Mass Spectrometry of Endogenous Proteins) which can elucidate physically-interacting co-regulators that may be required in establishing the functional specificity of your target protein. Together, these assays will provide you with multi-dimensional mechanistic insight into the factors and pathways involved in the response of your model system.



Active Motif Assay Connectivity. Mod Spec and ATAC-seq are both great assays for researchers who know little about the role of epigenetics in their disease or model system. Mod Spec will identify differential histone modifications that can then be profiled on a genome-wide level using ChIP-seq. ATAC-seq differentials can point to important transcription factors or histone modifications that that should next be profiled with ChIP-seq. RRBS adds the DNA methylation component and RIME identifies additional protein co-regulators that influence differential gene expression

Active motif assay connectivity.jpg

Collaborations in Precision Medicine: Building the World's First Data Commons in NAFLD/NASH

Tuesday, 26th June - 18:00 - Integrating Big Data - Amphitheater - Oral - Abstract ID: 40

Dr. Diane Harbison [1]

1. *Stratified Medicine Scotland Innovation Centre*

Stratified Medicine Scotland Innovation Centre (SMS-IC) is a unique consortium of partners, comprising the NHS in Scotland, 4 Scottish Universities and industrial partners across informatics and genomics (Aridhia Ltd and ThermoFisher Ltd). Close alignment and investment from these key stakeholders means that SMS-IC is able to bring together industry innovators, clinicians and world-class researchers to deliver precision medicine opportunities. This is achieved by linking Scotland's domain expertise, data assets and delivery infrastructure. The NASH Data Commons (NDC) is a unified data system that provides a comprehensive integrated knowledge system that will foster important discoveries in chronic liver diseases (CLD). Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of CLD with a global presence of 25 % and is the leading aetiology for liver transplantation, with strong links to life-style choices, such as type II diabetes and obesity. Early recognition and serial monitoring are as yet unmet but urgently required to prevent progression from steatosis to NASH, through to end-stage liver disease and associated complications.

In this presentation we will describe the key components in terms of expertise, delivery infrastructure and data assets that are being curated and developed to combine and build heterogeneous sets of data (see Figure). The NDC will combine imaging, genomic, biobanking and electronic health records (eHR) to provide a rich data set that can be used to augment the ability of disparate users to navigate complex data and to generate new data, insights and innovations.

One key aim of the NDC will be to provide insights into the hierarchy of importance of different pathways (metabolic/ fibrotic/inflammatory). Such insights will lead to the development of precision therapies. The NDC will be used to develop technologies and capabilities in four key areas: development of novel biomarkers, companion diagnostics, precision medicine clinical trials and to develop new therapeutics/treatment interventions that will require transformations of current clinical care pathways.

Implementing Preemptive Clinical Pharmacogenomic Testing at an Institution-Wide Level

Tuesday, 26th June - 18:20 - Integrating Big Data - Amphitheater - Oral - Abstract ID: 170

Dr. Cyrine Haidar [1], ***Dr. Mary Relling*** [1]

1. St Jude Children's Research Hospital

INTRODUCTION: The St. Jude Children's Research Hospital PG4KDS clinical trial opened in 2011 with the goal of providing a process to clinically implement preemptive pharmacogenomics. Pharmacogenomic test results are placed in the electronic health record (EHR) and coupled with interpretations and clinical decision support (CDS) alerts to guide treatment decisions across a number of therapeutic areas.

METHODS: Genomic DNA obtained from peripheral blood is genotyped using the PharmacoScan™ array (Affymetrix, part of ThermoFisher Scientific, Santa Clara, CA, USA; from 2011 to 2017, we used the DMET™ Plus array supplemented with a *CYP2D6*copy number assay). Clinical pharmacists place pharmacogenomic results and interpretative consults in the EHR. They also perform a medication assessment of the patient's current drug therapy regimen to screen for high-risk drug use. Active CDS alerts are customized for each gene-drug pair to include prescribing recommendations. Problem list entries for high-risk phenotypes in the EHR serve as discrete fields from which CDS alerts are generated. Genedrug pairs are prioritized for implementation based on availability of CPIC guidelines, primary evidence review, and with approval of an institutional oversight committee. Participants are asked whether they wish to be informed of their pharmacogenomic test results when they are released into the EHR, and once they turn 18 years old are asked to re-consent in order to remain on the protocol.

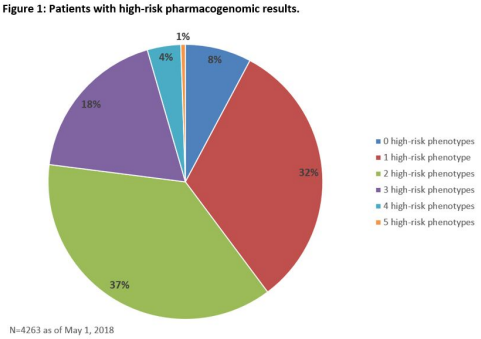
RESULTS: As of May 2018, eight genes (*CYP2D6, CYP2C9, CYP2C19, CYP3A5, DPYD, UGT1A1, TPMT, and SLCO1B1)*and 25 drugs have been clinically implemented (see www.stjude.org/pg4kds). Out of 4735 patients approached for participation, 4471 patients (94%) have consented to enroll in the PG4KDS protocol. The median age of patients was 8.9 years (range 0.17-51.92). Of these patients, 4030 (92%) have at least one high-risk pharmacogenomic result posted in the EHR. Most participants (96%) have requested to be informed of their test results, and out of 550 patients who were approached for re-consent when they reached the age of majority 535 (97%) consented to remain on the study.

DISCUSSION: The PG4KDS model for implementation of preemptive pharmacogenomics provides a successful example for pharmacogenomic testing on an institution-wide level.

Table 1: PG4KDS patient characteristics

Patient Characteristics (N=4471)	
Median age at PG4KDS enrollment (range)	8.9 years (0.17-51.92 years)
Female sex – no (%)	2043 (46%)
Race	
White – no (%)	2547 (57%)
Black – no (%)	1612 (36%)
Asian – no (%)	61 (1.4%)
Other – no (%)	251 (6%)
Primary diagnosis	
Oncologic Disease	*3199 (71%)*
- *Brain tumor*	1048
- *Leukemia/Lymphoma*	1210
- *Solid tumor*	941
Hematologic Disorder	1102 (25%)
Infectious Disease	149 (3.5%)
Other	21 (0.5%)

Patient characteristics.jpg



Patients with high-risk results.jpg

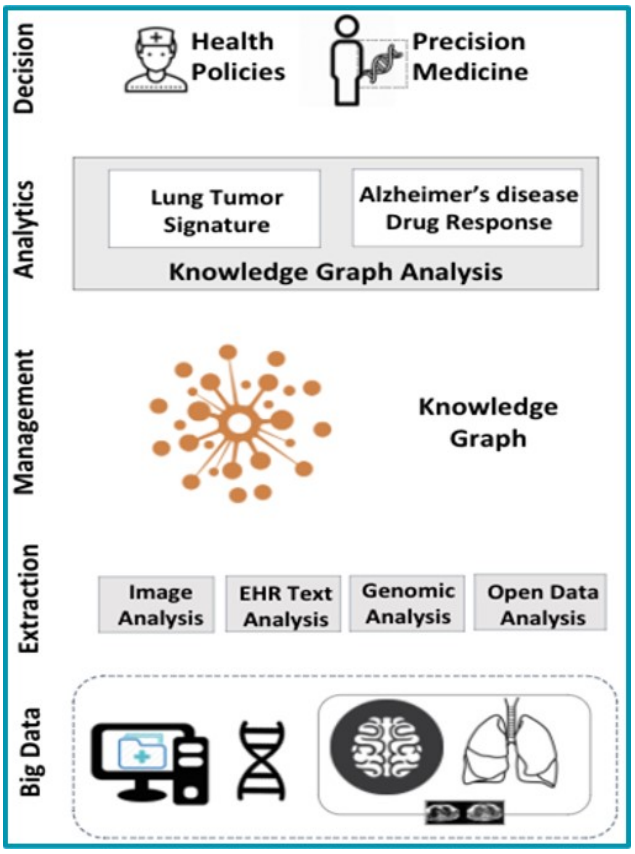
iASiS: Big Data to Support Precision Medicine and Public Health Policy

Tuesday, 26th June - 18:40 - Integrating Big Data - Amphitheater - Oral - Abstract ID: 130

Dr. Anastasia Krithara [1], Dr. Maria-Esther Vidal [2], Prof. Ernestina Menasalvas [3], Dr. Alejandro Rodriguez-Gonzalez [3], Dr. Eleftherios Samaras [4], Prof. Peter Garrard [4], Dr. Maria Torrente [5], Mr. Anastasios Nentidis [1], Dr. Grigorios Tzortzis [1], Dr. Vassiliki Rentoumi [1], Dr. Benjamin Lang [6], Mr. Nikos Dimakopoulos [7], Dr. Rui Mauricio [8], Dr. Alison Evans [8], Dr. Louiqa Raschid [9], Dr. Jordi Rambla De Argila [6], Prof. Gian Gaetano Tartaglia [6], Prof. Mariano Provencio Pulla [5], Dr. Georgios Paliouras [1]

1. *National Center for Scientific Research "Demokritos",* ***2.*** *Leibniz Universität Hannover,* ***3.*** *Universidad Politecnica de Madrid,* ***4.*** *St George's Hospital Medical School,* ***5.*** *Hospital Universitario Puerta de Hierro-Majadahonda,* ***6.*** *Centre for Genomic Regulation,* ***7.*** *Athens Technology Center,* ***8.*** *Alzheimer's Research UK,* ***9.*** *University of Maryland*

iASiS envisions the transformation of clinical, biological and pharmacogenomic big data into actionable knowledge for personalized medicine and decision makers. This is achieved by integrating and analyzing data from disparate sources, including genomics, electronic health records, and bibliography. The integration and analysis of these heterogeneous sources of information enables the best decisions to be made, allowing for diagnosis and treatment to be personalized to each individual. iASiS offers a common representation schema for the heterogeneous big data sources. Data resources for two different disease categories are explored: lung cancer (LC) and Alzheimer's disease (AD). **Methods:** The iASiS infrastructure converts clinical notes into usable data, combines them with genomic data, related bibliography, image data and more, and creates a global knowledge graph. The iASiS knowledge graph facilitates the use of big data analytics in order to discover useful patterns and associations across different resources. Employing novel inference techniques, the iASiS knowledge graph leads to the generation of new knowledge, by combining pieces of information that may not be apparent when examining each source separately. The final iASiS system will be a uniquely rich and up-to-date source of information, which would otherwise be fragmented into different sources. **Results:** The initial iASiS components tested against a rich data set of biomedical literature comprising more than 100,000 textual AD related sources yielded interesting initial results. In particular, when asked to provide appropriate treatment for AD patients based on the patients' genetic (allelic) status, the system identified alleles of risk with related treatments according to the current bibliography. Regarding LC, analysis on more than 170,000 clinical notes and 7,000 clinical reports from 706 patients revealed correlations between presence of risk factors, such as dyslipidemia, high blood pressure, smoking habit and COPD, and significant decrease in survival. Survival in females was significantly higher than in males, despite the smoking habit, stage and comorbidities. **Discussion:** iASiS will allow the generation of knowledge that will support precision medicine and more effective treatments for different diseases. The outputs from iASiS will have significant impacts on healthcare systems, ICT industry, individual patients and wider society.



Iasis framework.jpg

From cardiovascular genomics to interdisciplinary precision medicine

Wednesday, 27th June - 09:00 - Plenary speeches - Amphitheater - Plenary Speech - Abstract ID: 83

Prof. Anna Dominiczak [1]

1. *University of Glasgow*

Human primary or essential hypertension is a complex, polygenic trait with some 50% contribution from genes and environment. Richard Lifton and colleagues provided elegant dissection of several rare Mendelian forms of hypertension, exemplified by the glucocorticoid remediable aldosteronism and Liddle's syndrome. These discoveries illustrate that a single gene mutation can explain the entire pathogenesis of severe, early onset hypertension as well as dictating the best treatment.

The dissection of the much more common polygenic hypertension has proven much more difficult. The real breakthrough came with the initiation of the genome wide association studies (GWAS) characterised by a much more thorough coverage of the genome with thousands single nucleotide polymorphisms (SNPs). Typically 500,000 – 2,5000,000 SNPs have been used for the big, collaborative GWAS for hypertension. These studies resulted in several "hits" or signals with a genome-wide significance and a high level of reproducibility between studies. These "hits" have been used successfully to calculate genetic risk scores for cardiovascular complications such as left ventricular hypertrophy, stroke and coronary artery disease. Intragenic signals, such as for example Uromodulin, are being used to examine new pathways for cardiovascular protection and possibly new targets for drug discovery as well as new style stratified clinical trials.

The next steps in genomic medicine belong to a combination of the next generation sequencing (NGS) and/or other "omics" data followed by linkage with electronic health records, including preferably the real time clinical data, biochemistry, imaging, histology as well as longitudinal health outcomes.

Precision medicine involves examining the genetic makeup of patients and their differing responses to drugs designed to treat specific diseases. By building up an understanding of the 'strata' of responses and the genetics of the diseases, we hope to create more personalised and effective forms of treatment for groups of patients most likely to benefit. Significant past investment in Scotland in electronic health records (EHRs) and translational medicine research, coupled with a vibrant healthcare technology industry, positions Scotland as the location to drive forward the precision medicine agenda globally.

Figure 1 (modified from Aronson SJ & Rehm HL, Nature 2015;526:336-342) illustrates the precision medicine ecosystem as currently implemented in very few selected centres word-wide including our own. These modalities of precision medicine are ready for the prime time now.

References:

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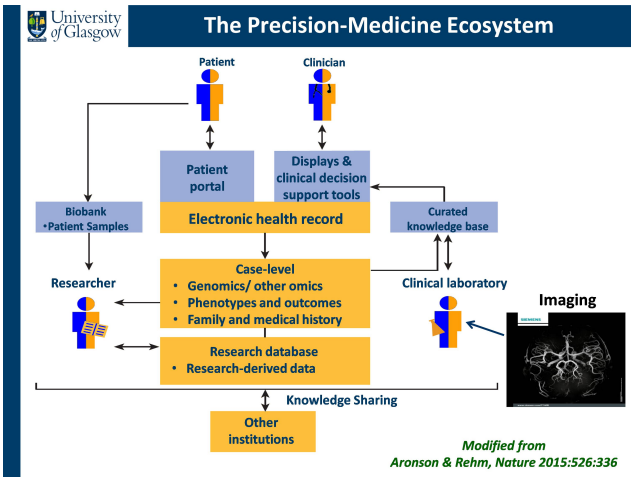


The precision-medicine ecosystem.jpg

Pharmacogenetics to Pharmaco-omics: Precision Medicine and Drug Response

Wednesday, 27th June - 09:40 - Plenary speeches - Amphitheater - Plenary Speech - Abstract ID: 98

Dr. Richard Weinshilboum [1]

1. *Mayo Clinic*

Introduction: Pharmaco-omics is the study of the role of “omics” science in providing insight into molecular mechanisms involved in individual variation in drug response phenotypes and mechanisms of drug action. Pharmaco-omics has evolved out of pharmacogenomics and involves a continuum from Discovery to Translation to Clinical Implementation.

Results: This presentation will describe both the effort of one large, highly integrated academic health center, the Mayo Clinic in the United States, to bring pharmacogenomics to the bedside and to clinically implement this aspect of genomic science that will eventually touch every patient everywhere. It will also, at the other end of the Discovery-Translation-Implementation spectrum, describe the results of pharmaco-omic studies of the selective serotonin reuptake inhibitor (SSRI) therapy of Major Depressive Disorder (MDD) to illustrate the use of pharmacometabolomics to inform pharmacogenomics to identify a series of novel genes that appear to play a role in individual variation in SSRI clinical response. Those genes include ERICH3, TSPAN5, DEFB1 and AHR.

Conclusions: This presentation will attempt to illustrate a range of “omics” research and clinical implementation strategies to move toward the goal of truly individualized drug selection and dosing, “Precision Medicine” as applied to drug therapy.

Treatment and cure strategies for WHIM syndrome immunodeficiency

Wednesday, 27th June - 10:45 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 30

Dr. Philip Murphy [1]

1. *NIH*

Gain-of-function mutations in chemokine receptor *CXCR4* cause the autosomal dominant immunodeficiency disorder WHIM syndrome. We have conducted a Phase 1 clinical trial of plerixafor, a specific CXCR4 antagonist, in patients with WHIM syndrome. Treatment was well-tolerated over 6 months and was associated with reduced infection frequency and wart burden. Interestingly, patient WHIM-09 was spontaneously cured in adulthood by chromothripsis (chromosome shattering) of one copy of chromosome 2, which fortuitously deleted the WHIM allele of CXCR4 and 163 other genes. In mice Cxcr4 haploinsufficiency was sufficient to phenocopy the apparent engraftment advantage of the chromothriptic HSC in WHIM-09. This suggests a mechanism for the patient's cure and a general cure strategy for WHIM syndrome by CXCR4 editing.

Precision medicine, challenges and opportunities

Wednesday, 27th June - 11:25 - Plenary Speeches - Amphitheater - Plenary Speech - Abstract ID: 180

Prof. Jacques S Beckmann [1]

1. *University of Lausanne*

The recent years have seen the emergence of both ground-breaking scientific developments in high-resolution, high-throughput data gathering technologies enabling cost-effective collection and analysis of huge, disparate datasets on individual health, as well as of sophisticated clinical bioinformatics or machine learning tools required for the analyses and interpretation of this wealth of data. These developments have triggered numerous initiatives in precision medicine (PM), a data-driven and currently still, essentially a highly genome-centric initiative (additional dimensions will, in due time, have to be integrated as well).

Proper and effective delivery of PM poses numerous challenges. Foremost, PM needs to be contrasted with the powerful and widely used practice of evidence-based medicine (EBM). The latter is informed by meta-analyses or group-centered studies from which mean recommendations are derived. These amount at first approximation to a “one size fits all” approach, whose major limit is that it does not provide adequate solutions for outliers. Yet, we are all outliers for one or another trait. In contrast to EBM, one of the strengths of PM, which focuses on the individual, lies in the area of personalized management, including of outliers.

To achieve these objectives, it will be necessary to bridge PM and EBM. Through the collection, analyses and sharing of standardized medically relevant data globally, evidence-based PM will shift progressively from therapy to prevention, thus leading eventually to improved, clinician-to-patient communication, citizen-centered healthcare and sustained well-being. We will discuss challenges and opportunities towards these goals.

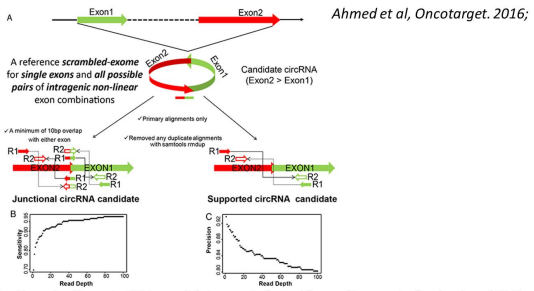
Integrated analysis of transcriptome and DNA sequence variation identifies genetic variants associated with circular RNA expression and their potential to contribute to disease risk

Wednesday, 27th June - 13:30 - Poster Session - Main hall - Poster - Abstract ID: 76

Dr. Ikhlak Ahmed [1], ***Dr. Joel Malek*** [1]

1. *Weill Cornell Medicine - Qatar (WCM-Q)*

Expression quantitative trait loci (eQTL) are genomic regions that influence RNA transcript expression levels and have potential to contribute at all major stages of gene regulation cascade. Circular RNAs (circRNAs), an emerging area of much research activity, with abundant presence in eukaryotic transcriptomes are linked to various human disorders and have not yet been studied for their association with genetic polymorphisms. We present an integrated analysis of circRNAs and genome sequence variation and show that circRNA expression is influenced by local single nucleotide polymorphic sites, referred to as circQTLs. These circQTLs exist independently of eQTLs with most circQTLs having no effect on mRNA expression. Only a fraction of the polymorphic sites are shared and linked to both circRNA and mRNA expression. Finally, circQTLs and eQTLs exist in separate linkage disequilibrium (LD) blocks with differential enrichments for functionally annotated features. The circQTL SNPs are highly enriched for human diseases and GWAS phenotypes and could potentially contribute to disease risk. This study reveals a previously uncharacterized role of the DNA sequence variation in human gene regulation and greatly improves our understanding of the mechanisms linking genetic variation to gene expression.



circRNA detection pipeline. circRNA candidates are inferred from alignment of paired-end RNA-seq data to a reference scrambled exome. Read-pair alignments that contain apparent backsplice junction are reported as either junctional or supportive evidence for the backspliced exon junctions. **B. and C. Sensitivity and Precision of circRNA detection pipeline.** Simulated reads at different read depths representing the expression level of randomly selected backsplice junctions mixed with a background of their canonical transcripts were run through the detection pipeline. Measurements of the correctly called circRNA junctions (true positives;TP), incorrectly called junctions (false positives, FP) and unidentified junctions (false negatives, FN) were used to define sensitivity and precision as TP/(TP+FN) and TP/(TP+FP), respectively.

Figure 1.jpg

Functional profiling of circular noncoding RNA circANKRD12 in cancer

Wednesday, 27th June - 13:30 - Poster Session - Main hall - Poster - Abstract ID: 78

Dr. Thasni Karedath [1], ***Dr. Ikhlak Ahmed*** [1], ***Ms. Fatima Al Dasim*** [1], ***Ms. Wafa Al Ameri*** [1], ***Dr. Joel Malek*** [1]

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ABSTRACT

Introduction: Circular RNAs (circRNA) that form through non-canonical backsplicing events of pre-mRNA transcripts are evolutionarily conserved and abundantly expressed across species. However, the functional relevance of circRNAs remains a topic of debate. Circular RNAs are unusually stable and abundant with tissue or developmental stage specific expression pattern. These qualities mark them to be a potential biomarker or a specific therapeutic target.

Materials and methods: Cancer cell lines (breast, ovarian and lung) used for the study. Silencing of circAKRD12 and its linear RNA was done using RNAi method and validated by using Real Time PCR method. Gene expression analysis was done using RNA-Seq analysis using illumina HiSeq 4000 system. Functional and phenotypic analysis were done by cell proliferation assays, cell cycle analysis and 3D organotypic cells generation on circANKRD12 silenced cells.

Results and discussion. In this study, we identified and characterized a circular RNA named circANKRD12 derived from Exon 2 and Exon 8 of the ANKRD12 gene, termed here as circANKRD12.This circANKRD12 was highly abundant in breast and ovarian cancers with two specific isoforms. The circANKRD12 is RNase R resistant and predominantly localized in the cytoplasm in contrast to its source gene mRNA. We confirmed the expression of this circRNA across a variety of cancer cell lines and provide evidence for its functional relevance through downstream regulation of several tumor invasion genes. Knockdown of this particular circANKRD12 affects several cell signaling pathways including cell cycle progression and immune modulatory pathways . We show that silencing of circANKRD12 induces a functionally relevant phenotypic change by significantly regulating cell cycle and increasing invasion and migration in cancer cells and shows an increased invasion through collagen gel in 3D spheroids.

These results reveal the functional significance of circANKRD12 and provide evidence of a regulatory role for this circRNA in cancer progression and can be a potential biomarker for either cancer diagnosis or prognosis.

Global DNA (hydroxy)methylation is not associated to MTX response at 3 months in early RA patients.

Wednesday, 27th June - 13:30 - Poster Session - Main hall - Poster - Abstract ID: 131

Ms. Helen Gosselt [1], ***Mr. Bertrand Van Zelst*** [1], ***Prof. Mieke Hazes*** [1], ***Prof. Robert De Jonge*** [2], ***Dr. Sandra Heil*** [1]

1. *Erasmus University Medical Hospital,* ***2.*** *VU University Medical Hospital*

Introduction: Methotrexate (MTX) is first-line therapy in early rheumatoid arthritis (eRA). ~20-40% of patients does not benefit from therapy and switch medication. Immediate effective therapy is crucial to restrain joint damage and achieve best response. Therefore, early biomarkers for MTX response are required. MTX interferes with the folate cycle, and might thereby indirectly inhibit methylation. 5-methyl cytosine (5mC) acts as gene expression regulator and can further oxidate into 5-hydroxymethyl cytosine (5hmC), also known to have gene regulatory functions. We investigated the association between changes in global DNA (hydroxy)methylation (Δ%5hmC and Δ%5mC) and MTX response (ΔDisease Activity Score28) over the first 3 months in eRA patients. **Method:**222 eRA patients were included from the Treatment in Rotterdam Early Arthritis Cohort (tREACH, ISRCTN26791028), a stratified, randomized clinical trial. Patients received triple (MTX + SSZ+ HCQ) or monotherapy (MTX) combined with corticosteroids and folic acid (10mg/wk). DNA was isolated from leukocytes at baseline (t0) and 3 months (t3) of MTX use and was degraded into single nucleotides using a DNA Degradase Plus enzyme. (Hydroxy)methylated cytosines (5hmdC/5mdC) were measured simultaneously using liquid chromatography- electrospray ionization-tandem mass spectrometry with multiple reaction monitoring (LC-ESI-MS/MS-MRM). Percentages of global DNA 5mdC and 5hmdC were calculated in relation to the total guanine concentration. Associations between ΔDAS28 and Δ%(hydroxy) methylation were adjusted for t0 DAS28 in a linear regression model. Paired analysis were conducted using a paired sample t test. **Results:**%5hmdC significantly increased during the first 3 months of MTX treatment (0.0364% at t0 vs 0.0372%, p=0.009). %Δ5hmdC was not associated to ΔDAS28 (B= -0.054, p=0.997). %5mdC did not change over the first 3 months of treatment (4.41% at t0 vs 4.40% at t3, p=0.393) and %Δ5mdC was not associated to ΔDAS28 (B= -0.570, p=0.220). **Discussion:**Our results suggest no role for global (hydroxy)methylation in relation to MTX response over the first 3 months in eRA patients. The role of increased %5hmdC during the first 3 months of MTX treatment needs further exploration.

Distribution of genetic polymorphisms of genes implicated in thiopurine drugs metabolism

Wednesday, 27th June - 13:30 - Poster Session - Main hall - Poster - Abstract ID: 52

Dr. Zohra CHADLI [1], ***Dr. Emna Kerkeni*** [1], ***Ms. Ibtissem Hannachi*** [1], ***Dr. Saoussen Chouchene*** [2], ***Dr. Nadia Ben Fredj*** [1], ***Dr. Amel Chaabane*** [1], ***Prof. Naceur Boughattas*** [3], ***Prof. Karim Aouam*** [1]

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Introduction:

Thiopurine-S-methyltransferase (TPMT) and inosine triphosphate pyrophosphatase (ITPA) are crucial enzymes involved in the metabolism of thiopurine drugs: azathioprine and 6-mercaptopurine, used in the treatment of several diseases, such as inflammatory bowel diseases and rheumatoid arthritis. Significant interethnic variation in the expression of *TPMT* and *ITPA* is caused by Single Nucleotide Polymorphisms (SNPs) of genes encoding these proteins.

Purpose

The aim of this study was to describe the distribution of *TPMT* and *ITPA* polymorphisms in Tunisian healthy subjects and establish accordingly, the metabolizer status of thiopurines drugs in this population.

Methods

A total of 309 healthy Tunisian subjects were recruited among blood donors. Informed written consent was obtained from all subjects. The genomic DNA was extracted using a salting-out procedure. *TPMT* (c.238G>C, c.460G>A and c.719A>G) and *ITPA* (c.94C>A and IVS2+21A>C) mutations were genotyping using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results

The observed frequencies of TPMT*3A and TPMT*3C alleles were 0.8% each. 299 subjects were homozygous for wild type gene and 10 were heterozygous. The phenotype distribution of TPMT was bimodal: 96.8% of subjects were extensive metabolizers (EX) and 3.2% were intermediate metabolizers (IM). Genotyping of *ITPA* revealed frequencies of 9% and 3% for IVS2+21A>C and c.94C>A mutations respectively. 233 subjects were homozygous for wild type gene, 73 were heterozygous and 3 were homozygous for variant alleles. Accordingly, a trimodal phenotype distribution was found: 75.4% of subjects were EM, 23.4% were IM and 1.2% were SM (slow metabolizers).

Conclusions

We have shown that *TPMT* allele frequencies distribution of our population are similar to that observed in African and Asian populations, while that of *ITPA* was similar to Caucasians. Combination of *TPMT* and *ITPA* has revealed that a quarter of Tunisian population have a reduced metabolic activity of thiopurines. Our results help to optimize thiopurine therapy by a pharmacogenetic approach in the context of personalized medicine.

Regulatory considerations on the evaluation of companion diagnostics (CDx) in Japan

Wednesday, 27th June - 13:30 - Poster Session - Main hall - Poster - Abstract ID: 133

Dr. Takayoshi Suzuki [1], ***Dr. Yoshinori Tsukumo*** [1], ***Dr. Arihiro Kohara*** [2], ***Dr. Mikihiko Naito*** [1]

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Introduction

CDx are getting very important in the drug development. Recent trends in developments and regulations of CDx in Japan will be introduced. A regulatory documents on the CDx has been released by the Ministry of Health Labor and Welfare (MHLW) in 2013, Additionally, two administrative notices, “Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products” and “Questions and answers (Q&A) on CDx and corresponding therapeutic products”, have been released. With these notification and administrative notices, Japanese regulation on CDx basically followed the principal of FDA to require co-approval of CDx with its related drug.

In addition, we introduce our approach to establish the reference cell lines for a validation of DNA sequence analysis for the NGS-based CDx. It is desirable to prepare a panel of cell strains with known mutations and provide a stable supply of standard materials

Methods

(Guidance documents)

A review committee was set up with members consisting of experts from industry, academia and government, together with concerned officers in PMDA, and MHLW. Then we classified the CDx based on their characteristics and extracted essential elements. Based on the discussions at the review committee, we prepared an evaluation criteria focused on the follow-on CDx,

(Standard materials)

Knock-in mutant cell lines were prepared by the Crisper/Cas9 method in the HEK 293/17T cell lines. Knock-in mutants were isolated by direct sequencing of approximately 150 colonies.

Results and Discussion

We have established two guidance documents as “Considerations on the evaluation criteria for clinical performance of the equivalent CDx against an existing product for 1) sequence determinations, and 2) pathological examinations”. The detail of these guidances will be introduced together with a general concept for bridging CDx from a prototype to a final product in the development process

We created new cell lines artificially introduced known mutations by genome editing techniques against clinically useful cancer-related genes. Finally, we obtained knock-in mutant cell lines for 32 cancer-related genes. These cell lines are available from the JCRB cell bank.

Table Number of the targeted knock-in mutants obtained by genome editing in HEK 293T/17 cell line

No.	gene	mutation	bp from PAM	Total Clones	Homo Knock-in	Hetero Knock-in
1	KRAS	35 G>A	4	160	0	2
2	NRAS	35 G>A	1	157	2	0
3	PIK3CA	1633 G>A	10	161	0	1
4	PTEN	697 C>T	7	156	0	1
5	TP53	743 G>A	5	159	2	2
6	JAK2	1849 G>T	8	164	3	1
7	FGFR3	746 C>G	1	167	0	1
8	KIT	2447 A>T	7	172	3	12
9	CTNNB1	121 A>G	6	164	1	0
10	CDKN2A	238 C>T	2	156	5	2
11	HRAS	183 G>T	2	172	2	5
12	KNSTRN	71 C>T	1	161	1	0
13	MAGOH	410 T>C	4	160	0	5
14	MDM2	994 C>T	6	171	0	2
15	EZH2	1937 A>T	7	153	4	0
16	IDH2	515 G>A	2	155	0	7
17	PDGFRA	2525 A>T	7	176	7	6
18	STAT3	1919 A>T	5	161	0	1
19	MTOR	6644 C>A	8	182	2	9
20	MET	3029 C>T	5	154	1	1
21	SMO	1234 C>T	8	157	8	7
22	NOTCH1	4799 T>C	9	167	0	2
23	ERBB3	310 G>A	4	171	0	1
24	DNMT3A	2645 G>A	6	149	0	1
25	BAP1	178 C>T	5	183	0	12
26	ALK	3824 G>A	4	190	4	5
27	MAP2K1	370 C>T	1	177	1	0
28	BRAF	1817 G>A	1	172	1	16
29	AKT3	232 C>A	2	192	0	5
30	BIM	585 G>C	1	192	6	9
31	IGF2	293 C>T	2	192	0	6
32	MYCN	1132 G>A	1	192	10	26

Table pemed2018 .jpg

Risk factors of isoniazid-induced hepatotoxicity in Tunisian tuberculosis patients

Wednesday, 27th June - 13:30 - Poster Session - Main hall - Poster - Abstract ID: 60

Dr. Nadia Ben Fredj [1], Dr. Zohra CHADLI [1], Dr. Amel Chaabane [1], Dr. Haifa Ben Romdhane [1], Dr. Najeh Ben Fadhel [1], Prof. Naceur Boughattas [2], Prof. Karim Aouam [1]

1. *Pharmacology Department, University Hospital, Monastir, Tunisia. Faculty of Medicine, University of Monastir, Tunisia.,* ***2.*** *Pharmacology Department, Faculty of Medicine, University of Monastir, Tunisia.*

Introduction: Previous studies have shown controversial results on whether slow acetylators or rapid acetylators cause isoniazid-induced hepatotoxicity (IIH).Moreover, the contribution of CYP2E1, a hepatic enzyme implicated in the formation of hepatotoxins, to the risk of developing IIH remains unclear.The objectives of this study were 1) to assess the risk factors of IIH occurrence, including demographic, kinetic and genetic factors and 2) to evaluate the extent of implication of the NAT2 and CYP2E1 polymorphisms genes in inducing this disorder. **Material and methods**: A total of 71 patients with tuberculosis receiving a conventional antituberculosis regimen were included. NAT2 and CYP2E1 genotypes were determined using PCR-RFLP. Therapeutic drug monitoring (TDM) of isoniazid was performed using Vivian's method. Cases of isoniazid-induced hepatotoxicity were diagnosed according to Benichou et al. Logistic regression was used to assess the relationship between each risk factor and the development of IIH. Univariate analysis, including demographic factors (age, weight, gender) and genetic factors (NAT2, CYP2E1 (1053C>T) and CYP2E1 (7632T>A) polymorphisms were performed separately for each risk factor, and then for combined (NAT2/CYP2E1) and (CYP2E1/ CYP2E1) genotypes. The variables having a p value less than 0.2 in the univariate analyses were included in the multivariate analysis model. Receiver Operating Characteristics (ROC) curve analysis was used to assess the cut_off values of factors showing a significant influence on IIH. **Results:** Eleven (15.4%) patients have developed IIH. Logistic regression has demonstrated that only CYP2E1 (7632T>A) gene polymorphisms was found to be a significant factor in IIH development (OR: 1.6; CI: 1.02-25.7)Multivariate regression including combined genotype has shown that the association of NAT2_Slow acetylor genotype and CYP2E1_C/D (7632T>A) was a risk factor of IIH (OR: 11.9;CI: 2.07-68.4). Moreover, Patients with both CYP2E1_C1/C1 (1053C>T) and CYP2E1_C/D (7632T>A) genotype have an increased risk of IIH (OR: 4.6; CI: 1.02-21.3). Also, INH concentration of isoniazid was found to be a risk factor of IIH, with a cut-off value over 3.69 mg/l (OR: 13.2, CI : 2,9-59), as shown by ROC analysis.**Conclusion:** TDM of isoniazid and the determination of both NAT2 and CYP2E1 genotypes could be useful for the prediction and prevention of IIH in Tunisian tuberculosis patients.

Towards precision anti-tumor vascular targeting therapy by lentiviral vectors carrying VEGFR2-specific nanobody

Wednesday, 27th June - 13:30 - Poster Session - Main hall - Poster - Abstract ID: 56

Dr. Roshanak Ahani [1], Dr. Hossein Etemadzadeh [1], Dr. Nasir Mohajel [1], Dr. Reza Ahangari Cohan [1], Dr. Mahdi Behdani [1], Dr. Farzin Roohvand [1], Prof. Kayhan Azadmanesh [1]

1. *Pasteur Institute of Iran*

Introduction: Cancer is one of the main causes of morbidity and mortality worldwide. Angiogenesis is general hallmark in the tumor growth and metastasis of cancers. Accordingly, therapies targeting angiogenesis and tumor vasculature (TV), such as vascular endothelial growth factor (VEGF)-targeted agents (like Bevacizumab which remains the only VEGF-targeted agent approved by the US Food and Drug Administration), are considered as the first-line treatment strategies for patients with metastatic cancers. Heterogeneity in primary tumor and related metastases however, similar to other anticancer therapies, demands precision and personalized therapeutic approaches for targeting TV, while lack of selectivity/specificity might impede their “systemic administration, too The tumor-associated endothelial cells (TAECs) are major cell type involved in tumor angiogenesis. The overexpression of vascular endothelial growth factor receptor-2 (VEGFR2 or KDR) in TAECs makes them a potent candidate for targeted therapy against cancer.

Methods: Several VEGFR2-targeted lentiviral vectors (LVs) pseudotyped with chimeric sindbis virus E2 glycoprotein (cSVE2s) were constructed. To this end, either sequence of a VEGFR2-specific nanobody (3VGR19) or its natural ligand (VEGF121) was inserted into the binding site of sindbis virus E2 glycoprotein (as fusogenic molecule). In addition, the corresponding LVs were constructed employing two transductional strategies, so called “chimeric” or “two molecules” strategies. For *in silico* modeling, FASTA sequence formats of cSVE2s were submitted to I-TASSER server. Other methods were based on regular protocols.

Results:*In silico* modeling data suggested that the inserted targeting motifs were exposed in the context of cSVE2s. Western blot analysis of LVs indicated the incorporation of cSVE2s into viral particles. Capture ELISA demonstrated the specificity/functionality of the incorporated cSVE2s. Transduction of 293/KDR (expressing VEGFR2) or 293T cells (negative control) by constructed LVs followed by fluorescent microscopy and flow cytometric analyses indicated selective transduction of 293/KDR cells (30 %) by both targeting motifs compared to 293T control cells (1–2 %).

Conclusions: These results implied similar targeting properties of VEGFR2-specific nanobody compared to the VEGF121 and still superior outcomes for two-molecule strategy and indicated the potential for transductional targeting of tumor vasculature by the nanobody displaying LVs which might be used as a carrier for precise/personalized delivery of Anti-TV therapeutics.

Diagnosis of Glioma Tumors Using Circulating Cell-Free DNA

Wednesday, 27th June - 13:30 - Poster Session - Main hall - Poster - Abstract ID: 46

. Vikrant Palande [1], ***Dr. Dorith Raviv Shay*** [1], ***Mr. Rajesh Detroja*** [1], ***Dr. Milana Frenkel-Morgenstern*** [1]

1. *The Azrieli Faculty of Medicine, Bar-Ilan University*

Introduction

Gliomas are the most frequent brain tumors, making up about 30% of all brain and central nervous system tumors, and 80% of all malignant brain tumors. Existing standard diagnostic technique for glioma tumor includes tissue biopsy, which is a highly invasive and hence a risky technique for the patient's survival. 'Liquid biopsy' is a new and recently developed non-invasive cancer diagnostic technique, which includes use of circulating cell-free DNA (cfDNA) fragments for tracing tumor markers. CfDNA fragments are one of those molecular bits that are released into the bloodstream after rapid apoptosis or necrosis of the tumor cells in the cancer patients. Our goal is to do comprehensive study between distinct types of glioma cancer tumors and cfDNA of the respective patients, to elucidate the scope of cfDNA in liquid biopsy technique for glioma diagnosis.

Methods

We collected 8 different glioma patient's tumor tissue and plasma samples and then isolated tumor DNA from glioma tumor tissue and circulating cell-free DNA(cfDNA) from the respective glioma patient's plasma. Isolated tumor DNA and cfDNA then deeply sequenced on Illumina HiSeq 2500 and then NGS data was analyzed to find out single nucleotide variants (SNVs) as well as structural variants on both cfDNA and tumor gDNA.

Results

We have successfully detected glioma specific mutations such as *IDH1*, *IDH2*,*PDGFRA*, *NOTCH1*, *PIK3R1*and *TP53*, from cfDNA isolated from the plasma of glioma patients and could relate this mutations to the different tumor grades of glioma. We are also studying the dynamics of these mutations in response to glioma drug treatment by collecting blood samples at different time intervals.

Discussion

This study may help in developing liquid biopsy technique for glioma tumor diagnosis and in its prognosis for monitoring the glioma treatment by non-invasive approach, and will eventually help physicians to decide the right treatment on appropriate time while bypassing the existing 'wait-and-see' approach of treatment monitoring.

Novel cancer gene variants and gene fusions of triple-negative breast cancers (TNBCs) reveal their molecular diversity conserved in the patient-derived xenograft (PDX) model

Wednesday, 27th June - 13:30 - Poster Session - Main hall - Poster - Abstract ID: 111

Ms. Jaeyun Jung [1], ***Prof. Suhwan Chang*** [1]

1. *1Department of Biomedical Sciences, University of Ulsan School of Medicine*

Despite the improved 5-year survival rate of breast cancer, triple-negative breast cancer (TNBC) remains a challengedue tolack of effective targeted therapy and higher recurrence and metastasis than other subtypes. To identify novel druggable targets and to understand its unique biology, we tried to implement 24 patient-derived xenografts (PDXs) of TNBC. The overall success rate of PDX implantationwas 45%, much higher than estrogen receptor (ER)-positive cases. Immunohistochemical analysis revealed conserved ER/PR/Her2negativity (with two exceptions) between the original and PDX tumors. Genomic analysis of 10 primary tumor-PDX pairswithIon-AmpliSeq CCP revealed high degree of variant conservation(85.0% to 96.9%) between primary and PDXs. Further analysis showed 44 rare variants with a predicted high impact in 36 genes including *Trp53*, *Pten*, *Notch1*, and*Col1a1*. Among them, we confirmedfrequent *Notch1* variant. Furthermore, RNA-seq analysisof 24 PDXs revealed 594 gene fusions, of which 163 were in-frame, including *AZGP1-GJC3* and *NF1-AARSD1*. Finally, western blot analysis of oncogenic signaling proteins supporting molecular diversity of TNBC PDXs. Overall,our report provides a molecular basis for the usefulness of the TNBC PDX model in preclinical study.

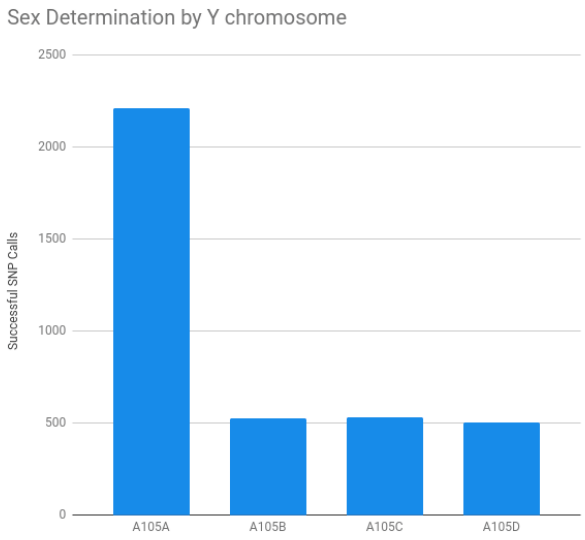
SVs have higher selection pressure to track inheritance by Y-Chromosome and mtDNA and associated paternal and maternal diseases respectively, while SNPs from them would be more individual specific

Wednesday, 27th June - 13:30 - Poster Session - Main hall - Poster - Abstract ID: 25

Dr. Abhishek Singh [1]

1. *University of Leipzig and Schiller International University in Heidelberg*

Structuralvariations, SVs, with size 1 base-pair to 1000s of base-pairs with their precise breakpoints and single-nucleotide polymorphisms, SNPs, were determined for members of a family. The amount of SNPs found in mtDNA was reasonably higher relatively speaking. It is also discovered that the mitochondrial DNA is less prone to SVs re-arrangements than SNPs which proposes better standards for determining ancestry and divergence between races and species, and accounts for maternally inherited diseases. Sex determination of an individual is found to be strongly confirmed by means of calls of nucleotide bases of SVs to the Y chromosome, which can also be a stronger criteria for Y-chromosome inheritance and associated paternal diseases. SVs would serve as a family line fingerprint of an individual for long term inheritance, compared to SNPs for short term inheritance contributing to his traits and drug responses.



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An integrative machine learning approach to identify the bio-markers of breast cancer treatment outcome

Wednesday, 27th June - 13:30 - Video Presentations - Web - Video - Abstract ID: 168

Mr. Huy Pham [1], ***Mr. William Klassen*** [2], ***Dr. Luis Rueda*** [2], ***Dr. Alioune Ngom*** [2]

1. *University of Dalat,* ***2.*** *University of Windsor*

Introduction. We applied a machine learning approach to identify bio-marker genes capable of predicting breast cancer outcomes including disease-free survival, and overall survival at 5 years and long-term, after a combination of the treatments: chemotherapy (CT), hormone therapy (HT), radiation therapy (RT), or no recorded therapy (NONE).

Method. The data from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC 2016), which contains gene expression of about 24500 genes and 1904 patients, was used to learn the classification model in backward elimination manner. First, support vector machine with linear kernel (SVM) is trained on the current set of features (genes), under 5-fold cross-validation scheme. Then, the feature with the lowest coefficients is removed. That procedure recursively repeats on the pruned set until the desired number of features to select is eventually reached. The final sets of genes are considered as potential biomarkers.

Results. For each treatment, we finally obtained a subset of 189 genes. The classification performances corresponding to seven combinations of treatments are presented in Figure 1. For the patients treated with CT and RT (CT=YES, HT=NO, RT=YES) we obtained the highest accuracy, about 98%. For the patients treated with CT only (CT=YES, HT=NO, RT=NO) the accuracy is the lowest, but still as high as about 90%. For each subset, about 15 to 26 genes are breast-cancer-related, about 55 to 65 genes are cancer-related, according to the list of 8016 cancer-related genes that we collected from various public resources. Among them, many genes associated with cancer-relevant pathways. They include: FGFR4, EGFR, MUC16, FGFR4, GSTP1, PLA2G2A, GPC3, DUSP1, PLA2G16, RUNX2, CDH1, CYB5A, CTGF, NCOA4, C1QB, CYB5A, CGA, ESR1, KIT, TAT, PYCARD, AIM2, SAA1, CEACAM1, ESR1, PPP1R1B, PRKAR1A, HPGD, TP63, TGFBR3, PGR, H19. For examples, the gene EGFR involve in the pathways “Inhibition of Signaling by Overexpressed EGFR”, “Signaling by Overexpressed Wild-Type EGFR in Cancer”, “PLCG1 events in ERBB2 signaling”. Or, the gene PGR involve in the pathway “Nuclear signaling by ERBB4”.

Conclusion. The results showed that our selected sets of genes could be considered as biomarkers for breast cancer survivability prediction.

Keywords: Breast cancer, survivability prediction, treatment, machine learning, bio-marker.

Genome Wide Association Studies Evaluating Response to Interferon Beta in Multiple Sclerosis: A Systematic Review

Wednesday, 27th June - 13:30 - Video Presentations - Web - Video - Abstract ID: 107

Mr. Ahmed Edris [1]

1. *Andalusia Group for Medical Services*

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating chronic inflammatory disease of the central nervous system. It affects up to 2.5 million people worldwide , representing a major cause of neurological disability in young adults.[1] Interferon beta(IF-B) has been used for decades as the initial therapy for relapsing remitting MS, it's recommended along fingolimod and glatiramer acetate as first line therapy options.[2] However, response to IF-B varies among patients with relapse reduction rates ranging from 30-50%. Identification of pharmacogenetic markers controlling response to IF-B may thus pave the way to predict a patient's response, aiming to achieve earlier control of MS symptoms, progression, and avoiding side effects.

Methods

A systematic review of GWAS evaluating response to IF-B was conducted according to PRISMA guidelines. A search strategy of PUBMED, GWAS Central, Google Scholar and manual search identified all published English language genome wide association studies evaluating response to IF-B in MS from 2000-2018. Selection criteria included: treatment with interferon beta for a minimum of 2 years and periodical neurological assessment of response using a validated scale (e.g: Expanded Disability Status Scale (EDSS) score).

Results Seven studies were initially selected for review, one was removed during the review process. The studies differed in their definition of a genome wide significant association(only two studies used the current accepted standard of $P < 5 \times 10^{-8}$). Several SNPS in genes potentially associated with response to interferon-beta (mainly involved in inflammatory pathways active in MS) were detected, including: GRIA3(significant SNPs in 2 studies), NINJ2, GPC5, HAPLN1, FHIT, GAPVD1, ADAR , IFNAR2 and an SNP within the human leukocyte antigen coding region.Three zinc finger proteins encoding genes were also associated with response (ZFAT, ZHFX4 and ZNF697). An association between a genetic variant in a SLC9A9 gene (influences T cells differentiation) and non response was also detected.

Conclusion

This review highlights the need for larger genome wide association studies, with larger sample sizes to validate significant gene associated with response to IF-B in multiple sclerosis. A meta-analysis of published studies may provide a mean of detecting genes with larger effects on patients' response.

A Multiparadigmatic Approach to Renal Disease and Kidney Preservation

Wednesday, 27th June - 14:30 - Drug target discovery and integration with individualized therapy / theragnosis - Amphitheater - Oral - Abstract ID: 137

Mr. Adam Alonzi [1], ***Mr. Apoorv Sharma*** [1]

1. *Knorm Inc.*

In this presentation we explore the latest developments in the burgeoning field of systems nephrology as it pertains to treating renal disease *in vivo* as well as the roles an assortment of factors play in improving or reducing transplant viability. The majority of alleles identified so far have weak correlations with their respective disorder or disorders. This has prompted nephrologists to begin studying miRNA function, DNA methylation, and proteomics alongside genomics. Phenomena associated with aging such as cellular senescence, the formation of glycation end products, autophagical decline, and mitochondrial dysfunction are also strongly implicated in common kidney disorders, and so will be useful in restoring healthy function in a living patient or salvaging a donor organ.

There are several open questions in nephrology, perhaps resolvable through the aforementioned areas of research, that point towards the need for a personalized approach pathogenesis and etiology (e.g. why does proteinuria not always correlate with the decline of kidney function?). Diving deeper into these problems and devising more nuanced classificatory systems can provide insights that will not only result in more effective treatments, but also in a greatly expanded donor pool. Alongside our review of the state of the art we also touch upon the potential usefulness of drug-predictive targeting software for developing polypharmacological molecules, as well as nanoparticle delivery systems designed with the compartmentalized structure of the kidney in mind.

Decoding cancer heterogeneity: Using an information-theoretic approach to design patient-specific drug combinations

Wednesday, 27th June - 14:50 - Drug target discovery and integration with individualized therapy / theragnosis - Amphitheater - Oral - Abstract ID: 66

Dr. Efrat Flashner-Abramson [1], ***Dr. Nataly Kravchenko-Balasha*** [1]

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Introduction

World-wide attempts are invested, aiming to develop effective strategies for personalized cancer medicine. We study a proteomic dataset obtained from ~3500 patients of 11 types. We aim to explore the data space of cancer patients and find a way to accurately classify tumors, such that every single tumor can be mapped precisely and unambiguously according to the molecular aberrations that it harbors.

Methods

We study cancer from an information-theoretical point of view. Using information-theoretic surprisal analysis we identify in each tumor protein unbalanced networks in which a regular flow of biological information is disturbed leading to a deviation of the tissue from the balanced "homeostatic" state (**Figure 1**). This imbalance governs the survival and progression of the tumors.

Results

We unraveled a surprisingly simple order that underlies the extreme complexity of tumor tissues, and demonstrated that only *17 unbalanced processes* characterize this large and diverse collection of tumors. Each tumor is described by a specific subset of 1-4 processes out of 17. We show that the majority of tumor-specific sets, named barcodes, are extremely rare, and are shared by only 5 tumors or less, supporting a personalized, comprehensive study of tumors in order to design the optimal combination therapy for every patient.We suggest that inhibition of the entire set of tumor-specific networks should stop the disease and significantly decrease the chances for the development of drug resistance.

We experimentally validated our approach using 10 different cancer cell lines. Using surprisal analysis each cell line was assigned a set of unbalanced processes and a combined drug therapy (**Figure 2**). Figure 2 shows that therapies predicted by us worked efficiently even in triple negative breast cancer cell lines, for which targeted therapy is currently unavailable.

Discussion

We present a novel approach to deal with the inter-tumor heterogeneity and to break down the high complexity of cancer systems into simple, easy to crack, barcodes (**Figure 3**). We sort the needles from the haystack, by identifying with high resolution patient-specific unbalanced processes and rewired signaling pathways. This deep understanding of tumor-specific imbalances should greatly advance the fields of cancer research and therapeutics.

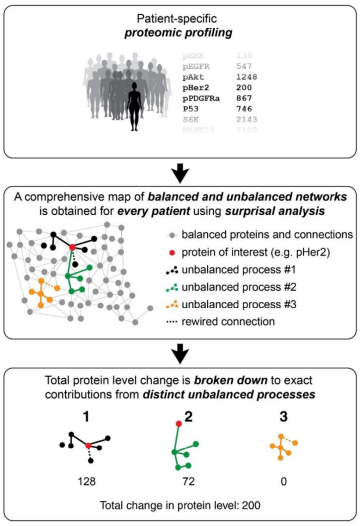


Figure 1. Surprisal analysis reveals accurate patient-specific unbalanced protein networks. Patient samples undergo proteomic analysis (upper panel), which is used as an input for surprisal analysis. The analysis uncovers a comprehensive map of unbalanced protein networks for every patient (middle panel), such that the contribution of every unbalanced process to the expression level change of each protein is easily deciphered (bottom panel: the total change in this simple illustration is 200: 128 due to process 1 and 72 due to process 2).

Figure 1 surprisal analysis reveals accurate patient-specific unbalanced protein networks.png

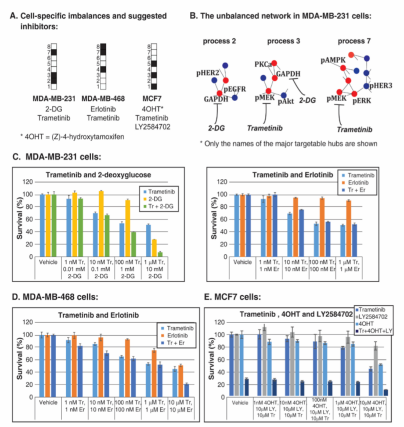


Figure 2. Validation of drug combinations that were predicted to be effective in breast cancer cell lines. Three breast cancer cell lines were selected for experimental validation: triple negative (**TNBC**) - MDA-MB-231 and MDA-MB-468, and luminal A MCF7. (**A**) A specific barcode for each cell line was constructed denoting the active unbalanced processes. Inhibitors against central targets were suggested for each process in every cell line (4OHT = activated form of tamoxifen). (**B**) For example, MDA-MB-231 cells harbor processes 2, 3 and 7. Central proteins with induced (red) or reduced (blue) levels relative to the balanced state are shown. Suggested inhibitors for those cells include **2-deoxyglucose** (**2-DG**, a glycolysis inhibitor) and **Trametinib** (**Tr**, a p-MEK inhibitor) (**C-E**) Experimental validation: A powerful effect was achieved when **Tr** and **2-DG** were combined to treat MDA-MB-231 cells **(C, left panel)**. Combining **Tr** with **erlotinib** (**Er**, a p-EGFR inhibitor, p-EGFR was not identified as a major target in these cells, see panel B) showed no superior effect as compared with trametinib alone (**C, right panel**). This combination was predicted to be effective in MDA-MB-468 cells. While each inhibitor alone killed only up to 50% of the cells, the combined treatment killed 80% of the cells **(D)**. Hence, the same combination of drugs was significantly less effective against MDA-MB-231 cells as compared with MDA-MB-468 cells, even though both cell lines are **TNBC**. (**E**) We predicted that a combination of **Tr**, **LY2584702** and **4OHT** should be effective against MCF7 cells. The combined treatment was indeed much more potent than each inhibitor alone.

Figure 2 validation of drug combinations.png

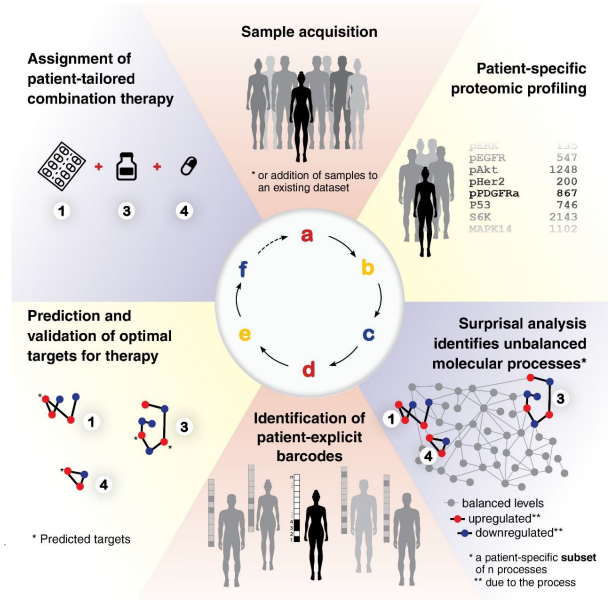


Figure 3. Workflow of our information-theoretic approach. Following acquisition of samples (a), a dataset is constructed using proteomics techniques (b). Suprisal analysis is then utilized (c) in order to uncover the complete patient-specific protein network structure, comprising balanced and unbalanced molecular processes, in which all molecules undergo coordinated changes in expression. Next, a patient-specific barcode is constructed, indicating *the set* of significant unbalanced processes that influence the specific tumor (d), and the tumor-specific unbalanced network is examined, aiming to identify and verify experimentally the major hubs whose blockage is suggested to lead to a collapse of the unbalanced network (e). Finally, a tumor-specific combination of targeted therapies is tailored to every patient (f)

Figure 3 workflow of our information-theoretic approach.png

Dendrimer-entrapped gold nanoparticles modified with beta-cyclodextrin for enhanced gene delivery applications

Wednesday, 27th June - 15:10 - Drug target discovery and integration with individualized therapy / theragnosis - Amphitheater - Oral - Abstract ID: 148

Ms. Jieru Qiu [1], ***Dr. Lingdan Kong*** [2], ***Prof. Serge Mignani*** [3], ***Prof. Anne-marie Caminade*** [1], ***Prof. Jean-pierre Majoral*** [1], ***Prof. Xiangyang Shi*** [2]

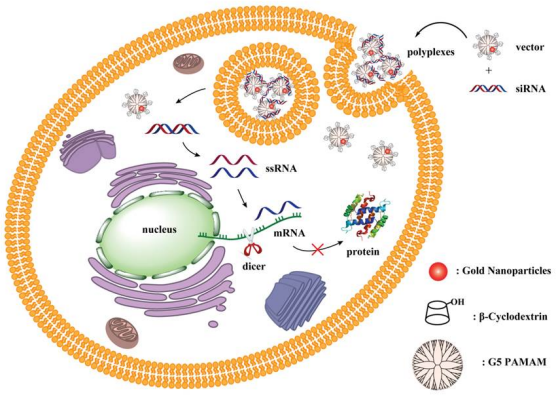
1. *CNRS-LCC TOULOUSE,* ***2.*** *Donghua University,* ***3.*** *Université Paris Descartes*

We describe a safe and highly effective non-viral vector system based on beta-cyclodextrin (beta-CD) modified dendrimer-entrapped gold nanoparticles (Au DENPs) for improved gene delivery applications. In our approach, we utilized amine-terminated generation 5 poly(amidoamine) dendrimers partially grafted with beta-CD as a nanoreactor to entrap Au NPs [1]. The acquired beta-CD modified Au DENPs (Au DENPs-beta-CD) were complexed with two kinds of plasmid DNA (pDNA) and two different types of therapeutic siRNA [2]. In preliminary experiments, the formed Au DENPs-beta-CD carrier has good cytocompatibility and enables efficiently cellular gene delivery for both pDNA and siRNA to the model cancer cells (Scheme 1). The developed Au DENPs-beta-CD may hold great promise to be used as an efficient vector system for enhanced gene delivery to different biosystems for therapeutic purposes.

[1] Qiu, J., Kong, L., Cao, X., Li, A., Tan, H., and Shi, X. (2016). Dendrimer-entrapped gold nanoparticles modified with beta-cyclodextrin for enhanced gene delivery applications. RSC Adv. *6*, 25633–25640.

[2] Qiu, J., Kong, L., Cao, X., Li, A., Wei, P., Wang, L., Mignani, S., Caminade, A.-M., Majoral, J.-P., and Shi, X. (2018). Enhanced delivery of therapeutic siRNA into glioblastoma cells using dendrimer-entrapped gold nanoparticles conjugated with beta-cyclodextrin. Nanomaterials *8*, 131. doi:10.3390/nano8030131

Scheme 1. Schematic illustration of the gene delivery process



Scheme 1.jpg

Integrated genomics of schizophrenia: finding a pathway to personalised medicine

Wednesday, 27th June - 16:00 - Multi-Topics - Amphitheater - Oral - Abstract ID: 132

Mr. Josh Atkins [1], ***Dr. Chantel Fitzsimmons*** [1], ***Prof. Murray Cairns*** [1]

1. *University of Newcastle*

SZ is a complex psychotic disorder that is currently diagnosed exclusively on clinical presentation. While many variants have been associated with the disorder, the challenge remains to develop diagnostics from this enormous amount of information. To overcome some of the barriers of complexity, we deploy a multidimensional approach based on the integration of genic risk for both SNPs and CNVs with known association to schizophrenia, with rare variants derived through whole genome sequence (WGS) analysis. Firstly, a logistic regression classifier approach was conducted to account for PRS for both SNPs and CNVs based of the PGC summary statistics. This was conducted on a cohort size of 433 cases, 302 psychiatrically screened controls and 1951 unscreened-controls. Combining both SNP and CNVs in a machine learning approach gave a better overall prediction compared to SNPs alone (area under the curve (AUC) + 2%). The best case prediction was achieved with respect to the psychiatrically screened control population (AUC 0.86). Loss-of-Function (LOF) variants derived from 335 cases and 165 controls were determined after the annotation of variant calls derived from 30 X WGS (illumina xTen). Variants were then filtered by constraint using probability of loss-of-function intolerance(pLI) extracted from the GnomAD database. These variants were further subjected to pathways analysis. While high pLI variants were not enriched in cases (p = 0.55, OR 1.08), pathways analysis suggested these were enriched in *neurodevelopmental disorders* and *schizophrenia.* In the absence of phenotypic association, effect prediction of genomic variation was further integrated using genomic annotation and allelic expression analysis through RNA sequencing in a smaller subset of samples (56 samples), to identify functional variants impacting on gene expression. This revealed quantitative impact of both rare CNVs and LoF variants on gene expression in individuals. Collectively, our integrative multidimensional approach was able to yield significantly more personalised insight into the systems biology of the disorder and expect this will ultimately account for the entire spectrum of variants across various effect sizes that will significantly impact the way we diagnose and treat schizophrenia

Implementing routine pre-emptive DPD testing with adaptive dosing to secure 5-FU administration: Performance in digestive and head-and-neck cancer patients

Wednesday, 27th June - 16:20 - Multi-Topics - Amphitheater - Oral - Abstract ID: 35

Dr. Manon Launay [1], ***Prof. Sebastien Salas*** [2], ***Dr. Laetitia Dahan*** [3], ***Prof. Jean-françois Seitz*** [3], ***Prof. Florence Dufaud*** [2], ***Prof. Bruno Lacarelle*** [4], ***Dr. Joseph Ciccolini*** [4]

1. *Laboratory of pharmacology - European Hospital Georges Pompidou,* ***2.*** *Medical oncology unit - La Timone,* ***3.*** *Digestive oncology Unit - La Timone,* ***4.*** *laboratory of pharmacokinetics - La Timone*

Introduction: Fluoropyrimidines are a mainstay in the treatment of numerous solid tumors. Most of the administered 5-FU dose will undergo extensive liver catabolism driven by dihydropyrimidine dehydrogenase (DPD). Drug dosing is particularly high in some settings such as digestive or head-and-neck cancers. DPD-deficient patients are likely to experience life-threatening toxicities. Those are now a rising issue regarding pre-emptive strategies to be undertaken to improve safety. 5-FU usually claims 20-40% of severe toxicities and up to 1% of toxic deaths.

Material and Methods: Prospective DPD testing was performed in 59 digestive and 240 head-and-neck cancer patients treated at La Timone University Hospital of Marseille. DPD status determination was performed on a phenotyping basis (i.e., UH2/U ratio measurement in plasma). Doses were tailored prospectively according to the recorded DPD status using an empirical geometric scale with reduction from 20 to 100% of standard 5-FU dosing. Toxicities were graded following CTCAE 2.0., efficacy following Recist criteria.

Results: DPD deficiency (PM patients) was suspected in 25% of digestive patients and 6% of head-and-neck patients. 5-FU dosing was subsequently cut by an average 35% and 20% in PM patients (2390±1225 mg vs 3653±1371 mg, p=0.003* in digestive cancer and 2102±254 mg/m² vs 2577±353mg/m², p<0.0001* in head-and-neck cancer). Overall, 10-12% of severe toxicities were reported, a value markedly lower than usually described with 5-FU. No early severe toxicities was observed in PM patients. Delayed severe toxicities were not significantly different between PM and non-DPD deficient (EM) (7% vs 7% in digestive cancer; 11% vs 13% in head-and- cancer). Of note, despite the reduction in dosing, no significant difference was observed between PM and EM in terms of efficacy (p=0.0893 in digestive cancer; p=0.2774 in head-and-neck cancer).

Discussion/Conclusion: This work demonstrates that basic DPD-based adaptive dosing of 5-FU achieves better efficacy–toxicity balance in patients with solid tumors. Of note, reducing 5-FU dosing in PM patients does not hinder treatment efficacy, while helps to avoid severe toxicities. Developing a proper PK/PD/PGx model should help in the future to tailor more precisely 5-FU dosing, so as to achieve a better optimization of the efficacy–toxicity balance of 5-FU.

A CMOS Chip NMR: The Next Generation of Molecular Phenotyping for Health and Disease

Wednesday, 27th June - 16:40 - Multi-Topics - Amphitheater - Oral - Abstract ID: 141

Dr. Weng Kung PENG [1]

1. *International Iberian Nanotechnology Laboratory*

In the early 90's, as the first human genome project was initiated, an extensive effort has been placed on mapping the role of genes in the onset of disease. Genetic contribution to different diseases however, were found to be varies and often very little, with non-genetic factors (e.g., environmental hazards, diet, microbiome) having much greater attributable risks, and thereby producing 'stochastically' large phenotypic pool. The key goals to understanding human health and disease depend on the success of translating technological innovations (e.g., molecular diagnostic, molecular imaging) into medical research (and eventually into clinical settings), and the ability to access the 'genotype-phenotype' correlogram through various omics-platform (e.g., proteomic, metabolomics, phenomics).

Our research focuses addressing the challenges (and unprecedented opportunities) by introducing a new generation of molecular phenotyping by rapidly mapping out the water-protein interactions (thus providing an 'inverse proteomic' information) within the microenvironment of biological fluids (e.g., blood, serum). We demonstrated that highly unique and specific 'molecular fingerprinting´ for disease diagnosis using a single drop of blood (<1μL) obtained in less than 10 minutes using our home-built portable NMR spectrometer. Some of our successful translational clinical works (and in the pipeline) includes the rapid and label-free malaria screening, rapid molecular phenotyping of oxidative stress in diabetes mellitus, and sub-stratification of endometriosis and molecular phenotyping in hemoglobinopathies.

- W.K. Peng, et.al., Micromagnetic resonance relaxometry for rapid label-free malaria diagnosis, Nature Medicine 20, 1069-1073 (2014)
- W.K. Peng, Chen, L. & J. Han, Development of miniaturized, portable magnetic resonance relaxometry system for point-of-care medical diagnosis, Review of Scientific Instruments 83, 095115 (2012)
- W.K. Peng, D. Lim, T.T. Ng & T.P. Loh, Two-dimensional T_1-T_2 Correlational Spectroscopy for Rapid and Label-free Molecular Phenotyping in Hemoglobinopathies, (Under-Reviewed, 2018).

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