PEMED 2020

Personalized and Precision Medicine

International Conference

BOOK OF ABSTRACTS

February 19-21

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Pharmacogenomics of Childhood Leukemia: From Discovery to Translation.

Wednesday, 19th February - 09:15: Plenary Speech: Precision Medicine (Auditorium) - Plenary Speech - Abstract ID: 141

Prof. Mary Relling [1], ***Prof. Williams Evans*** [2]

1. *St. Jude Children's Research Hospital,* ***2.*** *St. Jude Children's Research Hospital*

Coming soon

Precision Medicine Treatment of Diabetes

Wednesday, 19th February - 09:45: Plenary Speech: Precision Medicine (Auditorium) - Plenary Speech - Abstract ID: 91

Prof. Ewan Pearson [1]

1. *University of Dundee*

People are all different, and this is no different when we consider people with diabetes, yet the current approaches to management of diabetes tend to treat everyone the same. The field of precision medicine aims to recognise these differences – whether at the level of their phenotype or at the molecular level. Faced with multiple, and increasing, treatment options for diabetes as well as increasing healthcare costs there is a clear need to target therapy to maximise benefit and reduce harm for every patient with diabetes.

This talk will discuss advances in precision medicine and pharmacogenetics in diabetes over the last decade. I will initially outline striking examples seen in monogenic diabetes: subtypes of Maturity Onset Diabetes of the Young and for Neonatal Diabetes caused by potassium channel gene mutations, where patients are often able to transfer off insulin injections onto oral treatment. However, patients with monogenic forms of diabetes are rare, and this lecture will move on to how we might begin to tailor treatment in more common forms of diabetes – such as type 2 diabetes. I will then provide an overview of our latest understanding of the genetics of type 2 diabetes, where >400 variants have been identified and where extremes of the polygenic risk score are associated with considerable differences in diabetes risk. Partitioning genetic risk into component pathophysiological processes also allows us to start to predict progression of diabetes or drug response based upon the individual underlying diabetes aetiology.

There is increasing evidence that genetic and other molecular and clinical characteristics will impact on treatment outcomes. The exciting challenge now is how we incorporate this information into clinical care and establish that this improves patient outcomes.

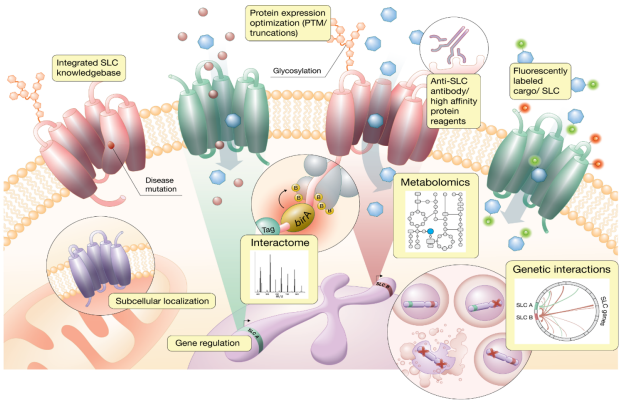
Shaping disease by modulating distribution of chemical substances

Wednesday, 19th February - 10:45: Plenary Speeches: Precision Medicine meets Technology (Auditorium) - Plenary Speech - Abstract ID: 89

Prof. Giulio Superti-Furga [1]

1. *CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences*

Management of chemical exchange across cellular membranes is critical to ensure access to nutrients, riddance of waste and safeguarding integrity and identity of the concerned biological (sub-)system (organelle, cell, organ, organism). Dedicated proteins are involved in the import of most chemical matter and expressed only when/where required, for energetic reasons, chemical safety and cellular homeostasis. Expression of particular membrane transporters repertoires should thus reflects demand-and-offer rules, integrating the metabolic aspiration of the systems with environmental availability. Regulation of the expression and function of solute carriers proteins (SLCs), the largest group of transporters in the human genome, should control cell metabolism and any process depending on it. If we were to know the transport specificity and function of most SLCs, their dynamic expression pattern could act as proxy for the metabolic state of the associated cell/tissue. We have started to systematically chart SLC function by genetics , proteomics and chemical biology. We find that SLCs modulate a large variety of cellular processes: such as metabolism, signalling, chromatin states, specific immune cell functions. We have systematically mapped the SLC genetic interaction map as well as a large survey of SLC-drug dependencies. We have also developed chemical tools allowing for the efficient regulation of individual SLCs. Altogether, these studies herald an age in which the interface between chemistry and biology can be studied, understood and modulated with unprecedented precision.



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Clinical epigenetics: seizing opportunities for translation

Wednesday, 19th February - 11:15: Plenary Speeches: Precision Medicine meets Technology (Auditorium) - Plenary Speech - Abstract ID: 130

Prof. Manel Esteller [1]

1. *Josep Carreras Leukaemia Research Institute (IJC)*

For the last twenty-five years an increasing amount of evidence has shown the relevance of epigenetics in cell biology and tissue physiology, being DNA methylation aberrations in cancer the flag-ship for the recognition of its disturbance in human diseases. From the candidate gene approaches, new powerful technologies such as comprehensive DNA methylation microarrays and whole genome bisulfite sequencing has recently emerged that have reinforced the notion of epigenetic disruption in the crossroad of many sickness. From the poster-boy cases of MGMT and GSTP1 hypermethylation in the prediction of alkylating drug response and prostate cancer detection, respectively, to the personalized treatment of leukemia with small molecules targeted to fusion proteins involving histone modifiers, the field has walked a long path. The current talk will focus in the epigenetic profiling, basically at the level of DNA methylation and histone modifications, that is starting to provide clinical value in the diagnosis, prognosis and prediction of response to drug therapies. For cancer, we have already a wide view of the undergoing DNA methylation events that expand beyond classical promoter CpG islands of tumor suppressor genes and we have a growing list of mutated chromatin remodeler genes that contributes to the tumorigenesis process. It is time to apply this knowledge in practical clinical situations like the diagnosis of cancers of unknown primary, the screening of malignancies in high-risk populations or a biomarker selection of the patients that should receive treatment with anticancer drugs. Beyond our comfort zone, we should be aware that chemical modifications not only affect the DNA molecule, but also RNA. The epigenetics of RNA or the analysis of the epitranscriptome represents another relevant step to understand the complex relationship between genotypes and phenotypes in human tumors.

Assessing the associations of the novel inflammatory marker GlycA with diabetes risk in a Mediterranean population, using both serum measures and a Mendelian randomization approach after a genome-wide screening

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 113

Dr. Oscar Coltell [1], ***Dr. Jose V. Sorlí*** [2], ***Ms. Rebeca Fernández-Carrión*** [2], ***Dr. Eva M. Asensio*** [2], ***Mr. Ignacio M. Giménez-Alba*** [2], ***Prof. Jose M. Ordovas*** [3], ***Prof. Dolores Corella*** [2]

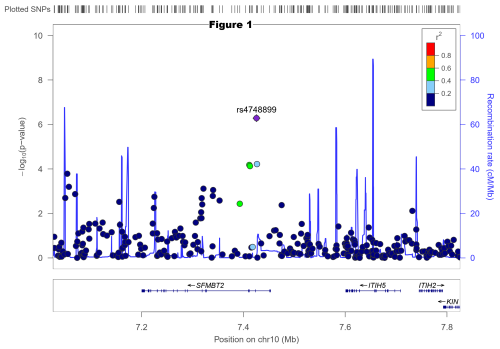
1. *Department of Preventive Medicine, School of Medicine, U. Valencia, Valencia / DLSI, Universitat Jaume I, Castellon / CIBEROBN, Madrid,* ***2.*** *Department of Preventive Medicine, School of Medicine, U. Valencia, Valencia / CIBEROBN, Madrid,* ***3.*** *Nutrition and Genomics Laboratory, JM-USDA Human Nutrition Research Center on Aging at Tufts University, Boston, USA / Department of Cardiovascular Epidemiology and Population Genetics, CNIC, Madrid, Spain / IMDEA Alimentación, Madrid, Spain*

Introduction. Recently, a novel proton nuclear magnetic resonance (NMR) spectroscopy signature has been characterized and named GlycA, which originates from the N-acetyl methyl groups of N-acetylglucosamine residues located on specific glycan branches of serum proteins. Circulating GlycA is an emerging biomarker that reflects inflammation through glycosylated acute phase reactants. This NMR-derived biomarker has been associated with higher type-2 diabetes risk in some studies, but more studies are needed in diverse populations. Currently, no study has been published evaluating the association between the serum GlycA biomarker and diabetes risk in the Mediterranean Spanish population. Moreover, Genome-wide association studies (GWAS) analyzing genes associated with this biomarker are very scarce. Our objectives are: 1) To investigate the relationship between serum GlycA concentrations and diabetes risk in a Mediterranean population; 2) To undertake an exploratory GWAS for serum GlycA, and 3) to select the top-ranked SNPs in a pilot Mendelian randomization approach for testing the association between GlycA genetic markers and diabetes risk in two cohorts from this population.

Methods. Serum GlycA was measured by NMR spectroscopy in 426 participants (38% diabetics) in the PREDIMED-Plus Valencia study (men and women aged 55-75, with metabolic syndrome). Fasting measures were carried out with a high□throughput NMR metabolomics platform (Nightingale Health Ltd, Finland), including other metabolites such as lipoprotein subclass profiling, etc. DNA genotyping was carried out using the Infinium OmniExpress genotyping array (Illumina). A GWAS for GlycA was undertaken (PLINK). Additive genetic models adjusted for covariates were fitted. In this exploratory analysis a $P<1x10^{-5}$ was set for statistical significance. The top-ranked SNPs were selected and tested for associations with diabetes and diabetes-related traits in this (PREDIMED Plus-Valencia) and in another cohort (PREDIMED-Valencia consisting of 1030 high-cardiovascular risk subjects, aged 67+/-7 years, 46% diabetics, also with GWAS genotyping. The top-ranked SNPs selected in the PREDIMED-Plus GWAS for GlycA were extracted and analyzed. Genetic risk scores (GRS), including top-ranked independent SNPs, were created. Associations of these SNPs with diabetes and diabetes-related traits were analyzed.

Results. Mean serum GlycA levels in the PREDIMED Plus-Valencia participants were 1.49+/-0.20 mmol/L, being statistically (P=0.003) higher in women than in men. In a multivariate-adjusted model, serum GlycA was significantly associated with diabetes (OR=4.12; 95%CI: 1.54-11-23; P=0,005 per mmol/L). Likewise, GlycA levels were significantly associated with higher BMI, higher triglycerides, lower HLD-c, as well as with a high-risk lipoprotein profile. In the GWAS for GlycA, we identified 11 SNPs at P<1x10-5, even after multivariate adjustment. These SNPs were located in genes related to inflammation: *SFMBT2*- rs4748899 (Scm Like With Four Mbt Domains 2), B= -0.071, r2=0.06, P=5.2E-07, MAF:0.47 (Figure 1 for the regional plot); *DAB1*-rs11207162 (Disabled-1), P=5.3E-07 (Figure 2); *TEK*-rs2208637 (Angiopoietin-1 receptor), P=3.6E-07 (Figure 3), among others.

Discussion. The genetic association of these individual SNPs and their GRS with diabetes and diabetes-related traits in both cohorts was less significant than for the GlycA levels, suggesting that more genetic variants should be identified and integrated into extended GRSs for better Mendelian randomization. Funding: Fundació La Marató de TV3 (538/U/2016); and Generalitat Valenciana (PROMETEO2017/017).



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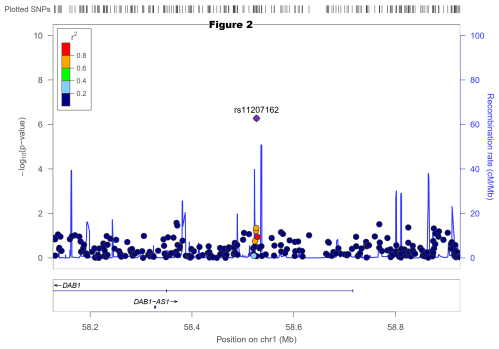

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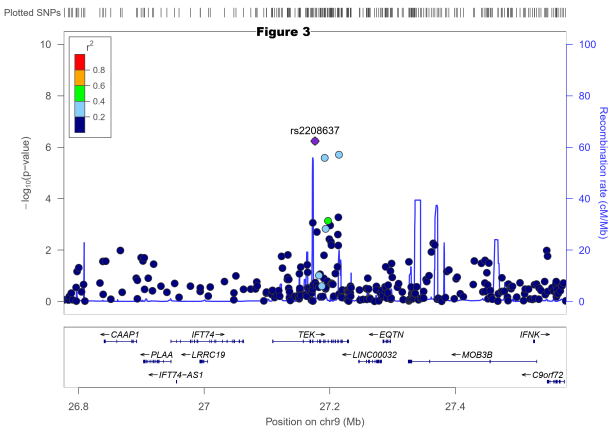

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Inverse association between the IRX3 (Iroquois Homeobox 3) gene rs3751723 polymorphism and obesity or type-2 diabetes in a high cardiovascular risk Mediterranean population

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 114

Prof. Dolores Corella [1], ***Dr. Carolina Ortega-Azorín*** [2], ***Dr. Carmen Saiz*** [2], ***Dr. Jose V. Sorlí*** [2], ***Dr. Ramon Estruch*** [3], ***Dr. Montserrat Fitó*** [4], ***Prof. Jordi Salas-Salvadó*** [5], ***Dr. Oscar Coltell*** [6]

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Introduction. Although the Fat Mass and obesity (*FTO*) gene (Chr.16) has been the gene most associated with BMI and obesity risk in multiple populations, the mechanism by which this gene can exert its function is not yet known. Some researchers have shown that the associations found in epidemiological studies with single nucleotide polymorphisms (SNPs) in the *FTO*gene, would not be due the *FTO*gene, but to the *IRX3*(Iroquois Homeobox 3) gene. The *IRX3*(Chr.16) gene is a member of the Iroquois homeobox gene family that appears to play multiple roles in the primary development of neural system. In animal models, several groups have reported functional links between the *IRX3*and the *FTO*. Thus, Ragvin et al., showed that noncoding sequences within *FTO*, influenced the IRX3, increasing the obesity risk and also the type-2 diabetes (T2D). Likewise, Smemo et al. reported that noncoding sequences of *FTO*interacted with the promoter region of the IRX3 gene, influencing gene expression at the brain level. However, in epidemiological studies, the association between IRX3 SNPs and obesity risk or T2D has been scarcely studied, and controversial findings have been reported. Therefore our aim was to analyze the association between a relevant polymorphism in the *IRX3*and anthropometric measures and T2D risk in a Mediterranean population.

Methods. We have analyzed participants in the PREDIMED study at baseline. PREDIMED is a multicenter study including high cardiovascular risk subjects (aged 67+/-7 years). Firstly we selected relevant SNPs in the *IRX3*gene according to the literature and genotyped the rs3751723 in the UTR 5 *IRX3*and the rs12445085 intergenic in the IRX3 in the PREDIMED-Valencia participants (n=1022). The *IRX3*: rs12445085 C>A was associated with bodyweight (P=0.007) and BMI (P=0.008), and this SNP was selected for further genotyping in other three sites on the East Mediterranean coast (Barcelona and Reus). Overall, n=3105 subjects (n=49% with T2D) were genotyped for the *IRX3*-rs12445085 SNP by TaqMan probes. We analyzed association with body mass index and T2D at baseline using linear and logistics regression models with adjustment for covariates and including interaction terms was indicated.

Results. Prevalence of the *IRX3*-rs12445085 C>A SNP was 54%CC, 38%CA and 8%AA. The minor allele was significantly associated with higher BMI ($p<0.05$) in the whole population even after adjustment for sex, age, field center, T2D and other covariates. This association was BMI higher in women than in men. When analyzing the association between the *IRX3*SNP and T2D, we observed that the minor allele was associated with lower diabetes risk, even after multivariate adjustment including BMI (OR: 0.89; 95%CI:0.80-0.99; P=0.043). This inverse association with obesity was higher in men, the interaction term SNP*sex being borderline significant (p=0.08).

Discussion. Studies analyzing the association between the *IRX3*polymorphisms and T2D in humans are scarce. These results and can help to explain the controversial associations between the *IRX3*polymorphisms and obesity and diabetes mimicking the effects of other variants also inversely associated with higher obesity risk and

lower T2D risk. Funding: Fundació Marató TV3 (538/U/2016).

Genetic polymormism profile associated with colorectal cancer in patients from Kazakhstan

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 115

Dr. Dmitriy Babenko [1], ***Prof. Valentina Sirota*** [1], ***Prof. Dana Tayzhanova*** [1], ***Dr. Yevgeniya Kolesnikova*** [1], ***Dr. Zauresh Tauesheva*** [1], ***Dr. Svetlana Kolesnichenko*** [1], ***Dr. Vera Zhumaliyeva*** [1], ***Dr. Anar Turmuhambetova*** [1]

1. *Karaganda Medical University*

Introduction: Colorectal cancer (CRC) is one of the major causes of mortality and morbidity, and is the third most common cancer in men and the second most common cancer in women worldwide. The incidence of CRC shows considerable variation among racially or ethnically defined populations in multiracial/ethnic countries. Understanding the multistage model of CRC involves understanding
the underlying genetic susceptibility in the population.
The aim of the study was to determine the genetic variation associated with CRC in patients in Kazakhstan.
Methods: Totally 267 patients with CRC diagnosed in Oncology hospital in Karaganda (KZ) and 87 persons as control were recruited. Genotyping of 75 SNPs (located in 50 different genes on 18 different chromosomes), associated with CRC, were performed by QuantStudio 12K Flex PCR and analyzed with Thermo Fisher Scientific Cloud service. Statistics were performed with R. Log-additive inheritance model were used for carrying out an association.
Results and discussion:267 patients aged from 24 to 87 (female (n = 126), male (n = 141)) and 87 people in control (female (n = 55), male (n = 32)) were analyzed.
We found that under log-additive genetic mode of inheritance rs4939827 (p = 0.002) and rs11190164 (p = 0.0007) had significant association with CRC. Using dominant mode of inheritance, rs11190164 was statistically highly significant (p = 0.001).
In control group, rs4939827 and rs11190164 were also in Hardy-Weinberg equilibrium (p = 1).
Minor allele of rs4939827 were detected in 26.4% cases and 15% - for rs11190164 in control group. In CRC group rs4939827 minor allele was in 46.3% cases, rs11190164 minor allele – 31.6% cases.
It should be noted that rs4939827 is risk factor and has clinical significance (114 publications in PubMed). CADD PHRED is 10.46. As for rs11190164, it is also found association with CRC in GWAS studies (3 publications in PubMed). CADD PHRED is 2.98.
Comparison minor allele frequency (MAF) distribution in Kazakh population and in other population showed that MAF of rs4939827 in Kazakh (0.26) is close to MAF in Han Chinnes (0.25) and Yoruba (0.24). As for MAF of rs11190164, Kazakh (0.15) and ALL population (0.16) have similar minor allele distribution.
Conclusion: It was found two polymorphisms (rs4939827, rs11190164) with CRC association in Kazakh population. We also determined that 13 polymorphisms associated with CRC before Bonferoni adjusting.
Research project № BR05236771.

Prediction Colorectal Cancer trained on genetic data of Kazakh population: Machine learning approach.

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 116

Dr. Dmitriy Babenko [1], ***Mr. Ilya Korshukov*** [1], ***Prof. Dana Tayzhanova*** [1], ***Prof. Valentina Sirota*** [1], ***Dr. Yevgeniya Kolesnikova*** [1], ***Dr. Irina Kadyrova*** [1], ***Dr. Vera Zhumaliyeva*** [1], ***Dr. Anar Turmuhambetova*** [1]

1. *Karaganda Medical University*

Intorduction: Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer-related death.
Approximately 5 to 10% of colorectal cancers are a consequence of recognized hereditary conditions.
Prediction of CRC based on genetic data by machine learning methods has been proposed as a promising platform for the development of genetic-based diagnostics.
The aim of the study was to analyze prediction ability of classification algorithms trained on genetic data of Kazakh population.
Methods: Totally 242 samples (177 from patients with CRC and 65 controls) were genotyped using CRC oncopanel (174 SNPs). 50% cutoff was chosen for QC variables and samples. NA values were replaced with imputing procedure using random forest approach. 20 supervised learning algorithms were used for training and evaluating, including deep learning approach like h2o. 80% and 20% data were randomly chosen for training and evaluation, respectively. Results on test (evaluation) data were used to estimate models.
Results: After QC procedure there were 214 samples and 146 variables (SNPs). Train data contains 120 CRC and 40 controls, validate data – 40 CRC and 14 controls.
H2ODL, H2ORF, POLYMARS and RF reached 100% sensitivity.
CTREE, SVM, MARS and MULTINOM reached 98%, 57%, 50% and 50% specificity, respectively.
CTREE, SVM, MARS and GLMNET had 99%, 85%, 83% and 81%
PPV, respectively.
H2ODL, RF, ADABOOS and SGD had 100%, 100%, 60% and 60%
PPN, respectively.
CTREE, H2ODL, RF and MARS obtained 80%, 78%, 78% and 78% accuracy, respectively.
Average sensitivity on all models was 88%, specificity – 34%, PPV -89%, PPN – 55%, accuracy – 74%
Discussion and Conclusions: It was determined that Conditional Inference Trees (CTREE, Hothorn and Zeileis, 2015) showed the best balanced results with 98% sensitivity and 74% specificity.
Overall classification models showed either high sensitivity or high specificity
We further suggest that continued comprehensive sampling and incorporation of up-to-date genetic and oncology data into model training will be crucial to the clinical utility and sustainability of machine learning-based molecular diagnostics.
Research project № BR05236771.

Seroprevalence of Transfusion-Transmissible Infections among Blood Donors in the Central Region of Saudi Arabia

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 2

Dr. Waleed Alabdulmonem [1], ***Mr. Fahad Abaalkhail*** [1], ***Mr. Faisal Alzaaqi*** [1], ***Mr. Abdulhakeem Aloqla*** [1], ***Mr. Abdullah Alsamaany*** [1], ***Mr. Azzam Alsughayyir*** [1], ***Mr. Sulaiman Alodhaylah*** [1], ***Mr. Rayan Aldoubiab*** [1], ***Mr. Saleh Alhammad*** [1], ***Mr. Abdullah Al-musallam*** [1], ***Dr. Fuhaid Alqossayir*** [1], ***Dr. Ali Shariq*** [1], ***Dr. Zafar Rasheed*** [1]

1. *Qassim University*

Objectives: Blood and blood products screening is an important tool to decrease the onset of transfusion-transmitted infections (TTIs). TTIs varies from region to region depending on the blood donors load. This study was aimed to determine the seroprevalence of TTIs among blood donors at Buraidah Central Hospital Blood Bank, Buraidah, Central Region of Saudi Arabia. Methods: This is a cross-sectional study performed on the blood donors'records from March 2017 to December 2018 at Buraidah Central Hospital Blood Bank. A total of 2295 blood donors were screened for serological tests for hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HbcAg) total, hepatitis C virus (HCV), human immunodeficiency viruses (HIV), rapid plasma reagin (RPR), and human T-lymphotrophic virus-1 (HTLV-1). Results: Out of 2295 blood donors, O positive blood group was found to be highest (42%), followed by A positive (23.4%), B positive (20.9%), O negative (5.45%), AB positive (3.4%), A negative (2.8%), B negative (2.1%) and AB negative (0.5%). Moreover, the total number of Rh-negative donors was significantly lower as compared with Rh-positive. Seroreactive tests were found to be positive in only 1.002% of all studied donors, among them HbcAg total was the highest (0.784%), followed by HBsAg, HCV and RPR. Whereas all tested donors were found to be negative for HIV and HTLV infections. Conclusions: This study clearly determined significantly lower rate of seropositive TTIs among the studied blood donors but larger scale studies at molecular level are required to improve the knowledge and to prevent the seropositive occurrence of TTIs.

Subtypes of lipopolysaccharide activate inflammatory signalling via cluster of differentiation-14 and toll-like receptor-4 in human monocytic cells

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 3

Dr. Waleed Alabdulmonem [1], ***Dr. Zafar Rasheed*** [1], ***Dr. Hussain Alssadh*** [2]

1. *Qassim University,* ***2.*** *Department of Molecular Medicine, University of Essex, United Kingdom,*

Background: The cellular component of innate immunity relies on cluster of differentiation (CD) 14 and toll-like receptor (TLR)-4 to combat harmful pathogens.
Aims: To investigate the effect of lipopolysaccharide (LPS) subtypes smooth (O55:B5) and LPS rough (EH100) on the expression of CD14 and TLR-4 in human monocytic (THP-1) cells.
Methods: Monocyte to macrophage differentiation was achieved in THP-1 cells by phorbol-12-myristate-13-acetate (PMA) treatment. Surface expression of CD14 and TLR-4 were determined by flow cytometry after treatment with LPS subtypes. TNF-α was measured by ELISA. Confocal microscopy was used to determine colocalization of CD14 and TLR-4 receptors on THP-1 cell surface.
Results: Treatment of THP-1 cells with LPS subtypes significantly increased the expression of CD14 and TLR-4 receptors ($p<0.05$). Higher levels of TNF-α were released in LPS-subtypes stimulated cells but the differences in the levels of TNF-α in differentiated cells and undifferentiated cells still unclear. Colocalization showed positive correlation between CD14 and TLR-4 receptors ($r>0.83$).
Conclusions: This study revealed that monocyte to macrophage differentiation in THP-1 cells increases the surface expression of CD14 and TLR-4 receptors and also leads overproduction of TNF-α.

Tailoring type II diabetes treatment: 5-HTTLPR and VNTR STin2 polymorphism and metformin efficacy

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 21

Mr. Taichi Ochi [1], ***Prof. Petra Denig*** [1], ***Prof. Hiddo Lambers Heerspink*** [1], ***Prof. Eelko Hak*** [1], ***Prof. Bob Wilffert*** [1]

1. *University of Groningen*

Aims: Serotonin transporter (5-HTT) has been associated with metformin intolerance and may play a role in its efficacy. Our investigation focuses on the effect of 5-HTTLPR and VNTR STin2 genotypes on metformin efficacy by measuring HbA1c levels after six months of metformin initiation.

Method: 320 participants of PROVALID (PROspective cohort study in patients with type 2 diabetes mellitus for VALidation of biomarkers) within the GIANTT (Groningen Initiative to Analyse Type 2 Diabetes Treatment) cohort who initiated metformin were genotyped for combined SERT 5-HTTLPR/rs25531 (L*L*, L*S* and S*S*) and 5-HTT VNTR (STin2.9/10 and STin2.12).

Descriptive statistics of patient characteristics split by 5-HTTLPR genotype were summarised and significance was determined by ANOVA and Kruskal–Wallis tests. Multivariate linear regression determined whether 5-HTTLPR/VNTR genotype affected metformin efficacy by change in Hb1Ac level from baseline to six months, adjusted for age, sex, index Hb1Ac, serum creatine at index, metformin dosage and concomitant use of medications that may affect metformin efficacy. The covariates were determined by preliminary univariate linear regression.

Results: Of the 320 participants, 184 men and 136 women were studied, with an age of 58.6 ± 8.6 (year) and index HbA1c of 58.6 ± 14.4 (mmol/L). 5-HTTLPR was characterized in 94 patients as L*L*, 150 patients as L*S* and 76 patients as S*S* genotype. HbA1c levels at six months between 5-HTTLPR was found to be 49.7 ± 8.1 for L*L*, 51.1 ± 12.2 for L*S* and 50.5 ± 7.1 (mmol/L) for S*S*. VNTR STin2.12 was categorized in 231 patients, while STin2.9/10 was found in 89 patients.

Unsurprisingly, baseline HbA1c and metformin dosage were significantly associated with HbA1c response at six months. Adjusted for these and other confounders, our prediction model found 5-HTTLPR L*S* patients to have higher Hb1Ac levels at six months from baseline than L*L* patients (B= 2.33, p = 0.031) but not in S*S* patients (B= 1.18, p = 0.325). 5-HTT VNTR STin2 was not found to be a significant predictor for HbA1c response at six months.

Conclusion: 5-HTTLPR genotyping may assist L*S* patients, but not 5-HTT VNTR genotyping, in determining metformin efficacy over the course of six months. Antidepressant treatment was not found to be associated with 5-HTTLPR response, therefore not found to be associated with affecting metformin efficacy within our patient cohort.

Reassessment of complex CYP2D6 Alleles: functional Impact of individual SNPs and Haplotypes

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 29

Dr. Kathrin Klein [1], ***Dr. Kyoko Momoi*** [1], ***Prof. Ulrich M. Zanger*** [2]

1. *Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology,* ***2.*** *Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology Stuttgart and Eberhard-Karls-University, Tuebingen*

Introduction

CYP2D6 is a highly polymorphic enzyme metabolizing 20-25% of all clinically used drugs. More than 100 allelic variants result in four distinct phenotypes commonly referred to as ultrarapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM). Urinary metabolic ratio of sparteine (MR_S) is a suitable marker for classification of 2D6 metabolizer phenotype occurring in a multimodal distribution. A far-distant enhancer polymorphism and new haplotypes (Wang et al., 2015) inspired us to re-investigate genotype-phenotype relationships of the two related alleles **2*(2850C>T, 4180G>T), *in vivo* correlated to the EM phenotype, and **41* (additional variant 2988G>A), *in vivo* correlated to the functionally impaired IM phenotype (Raimundo et al., 2004).

Methods

Individual variants or various combinations of 2850C>T (R296C), 4180G>T (S486T) and 2988G>A (intron 6) were introduced in minigene constructs and expressed in COS1 and Huh7 cell lines. Recombinantly expressed CYP2D6 activity was measured using propafenone as substrate, protein expression was quantified by western blot and transcripts were quantified by specific Taqman assays.

Results

Both 2850C>T and 2988G>A reduced activity and protein levels similarly by ~50-65% compared to the reference allele **1* (100%), whereas the combination of both variants resulted in only ~20% residual protein and activity. In contrast, SNP 4180G>T restored activity and protein levels to normal on both double-variant haplotypes (2850+4180 and 2988+4180), but not on the triple-variant haplotype (2850+2988+4180), which was functionally similar to the **41* allele. Effects on the transcript level corresponded well to the protein/activity levels.

Discussion

These data indicate that triple-variant haplotypes have to be considered to explain the functional differences between the EM allele **2* and the impaired IM allele **41*. While the unexpected loss of function due to 2850C>T can be rescued by 4180G>T (mimicking the EM phenotype of **2*), the additional intronic 2988G>A variant in the triple variant cannot not be completely rescued, thus resulting in the impaired IM phenotype. Our data are furthermore compatible with aberrant splicing being involved in these phenotypic differences.

References

Wang D et al. (2015). *Human Molecular Genetics 24, 1556–1562*

Raimundo et al. (2004). *Clinical Pharmacology and Therapeutics 76, 128-138*

The study was supported by the Robert Bosch Foundation, Stuttgart, Germany

Genome-wide copy number analysis identifies AKT as new therapeutic target for malignant pleural mesothelioma

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 51

Dr. Claudia Kalla [1], ***Mrs. Dina Moench*** [2], ***Mrs. Maithily Ranjan*** [2], ***Dr. Alessandro Pastore*** [3], ***Dr. Sabine Bode-Erdmann*** [4], ***Prof. Hans-Georg Kopp*** [5], ***Prof. German Ott*** [6]

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Introduction: Malignant pleural mesothelioma (MPM) is a neoplasm with inferior prognosis and notorious chemotherapeutic resistance. Targeting aberrantly overexpressed kinases to cure MPM is a promising therapeutic strategy. Here, we intended to identify suitable therapy targets by i) detecting recurrent chromosomal gains associated with MPM, ii) specific inhibition of amplified and overexpressed kinases in MPM cells.
Methods: Primary MPM were screened for chromosomal gains and losses using OncoScan technology. The biological significance of AKT expression was assessed in primary MPM by immunohistochemistry using AKT1, AKT2 and AKT3 antibodies. MTT (3,(4,5-dimethylthiazol-2)2,5 difeniltetrazolium bromide) assay was used to examine the cell viability upon treatment of MPM cell lines (derived from patient-derived MPM xenografts) with ipatasertib alone and in combination with PI3K/mTOR inhibitors.
Results: Genomic profiling of 42 primary MPM revealed 12 significant gain regions. Among them, 14q32.33 and 19q13.2 gain affected AKT1 and AKT2, two members of the AKT serine/threonine protein kinase family. Protein expression of all three AKT kinases was detected in the vast majority of 68 MPM patient tumors: 75.5% MPM expressed AKT1, 83.3% AKT2, 98.5% AKT3, and a total of 70.6% MPM co-expressed AKT1/AKT2/AKT3. We tested the therapeutic effect of the selective pan-AKT inhibitor ipatasertib on three MPM cell lines expressing different AKT isoformes. Ipatasertib treatment resulted in a dose-dependent growth inhibition, without obvious relationship between the cell line's sensitivity and the expression of certain AKT isoformes. Furthermore, ipatasertib significantly enhanced the antitumor effect of mTOR inhibitors (rapamycin, INK128) and PI3K/mTOR inhibition (BEZ235).
Discussion: Our study demonstrates recurrent activation of AKT kinases by copy number gain and upregulated expression in MPM. Treatment with the AKT inhibitor ipatasertib alone or in combination with PI3K/mTOR inhibitors is effective in suppressing MPM cell growth and should be further explored as a therapeutic alternative in mesothelioma.

CRISPR/Cas9 mediated genome editing of cytochrome P450 reductase (POR) in HepaRG cells

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 57

Mrs. Tamara Heintze [1], ***Dr. Kathrin Klein*** [1], ***Prof. Ulrich M. Zanger*** [2]

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Background: Novel developments in CRISPR technology (Clustered Regularly Interspaced Short Palindromic Repeats) and CRISPR-associated RNA guided Cas9 endonuclease (CRISPR/Cas9) open promising possibilities for specific genome editing. However, the application of this technology in metabolically competent cells like primary human hepatocytes or cell models like HepaRG is difficult because of their limited life time or required differentiation process. As an example for genome editing we chose cytochrome P450 reductase (POR) as a target, which is a ubiquitous microsomal electron transport protein essential to cytochrome P450 (CYP) – mediated biosynthesis of endogenous substrates like sterol and bile acid as well as oxidative metabolism of xenobiotics. POR is expressed at a much lower stoichiometrical level than CYPs and is expected to be a limiting factor for CYP activity. With the CRISPR/Cas9 induced knockout in the metabolically competent cell line HepaRG we were able to investigate the impact of variable POR levels on individual CYP activities and other cellular functions of POR.

Methods: To ensure efficient knockout of POR two guide RNAs (gRNA) located in exon 2 and 4 were designed to introduce double strand breaks using CRISPR DESIGN (http://crispr.mit.edu/), and inserted in lentiCRISPRv2 vector system (Addgene). The individual lentiviral constructs were transduced into undifferentiated HepaRG cells which were subsequently selected by puromycin treatment. POR knockout was evaluated by western blotting, mRNA analyses as well as POR activity measurements (cytochrome C reduction assay). CYP-substrate cocktail assay with mass-spectrometric quantification was used to analyze functional effects on CYP enzymes of families 1, 2 and 3. Quantification of mRNA panels representing various gene classes was performed by qPCR (Fluidigm).

Results:POR gene disruption in HepaRG cells was detected by T7E1 assay for both gRNAs and resulted in loss of POR protein and mRNA by 60 to 80%, dependent on the gRNA used. The transduced cells could be differentiated and were morphologically similar to the parent HepaRG cells. At higher residual POR activity (~40%), all CYP activities except CYP2C8 were decreased between 20 and 70%. At lower residual POR activity (~20%), all CYP activities were decreased up to 95%. POR knockdown also had differential effects on mRNA expression, resulting in upregulation for some genes (e.g. CYPs 1A1/2, 2C8) and downregulation of others (e.g. CYPs 2E1, 2C9).

Conclusion: The POR knockout cells give us the possibility to further investigate the regulatory mechanisms and functional impact of POR on CYPs as well as other POR targets. This cell-batch based CRISPR/Cas9 method can now be applied to target other genes in HepaRG or other metabolically competent cells like primary human hepatocytes.

Acknowledgement: Supported by the Robert Bosch Foundation, Stuttgart, Germany.

Panel-based genetic analysis of somatic variation in distant metastases of primary renal cell carcinoma

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 56

Mrs. Carolin Meyerhoff [1], ***Dr. Viktoria Stühler*** [2], ***Dr. Anna Reustle*** [1], ***Dr. Florian Büttner*** [1], ***Dr. Pascale Mazzola*** [1], ***Mr. Siarhei Kandabarau*** [1], ***Dr. Stefan Winter*** [1], ***Mr. Jörg Hennenlotter*** [2], ***Dr. Steffen Rausch*** [2], ***Prof. Jens Bedke*** [3], ***Prof. Matthias Schwab*** [4], ***Dr. Elke Schäffeler*** [1]

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Introduction:
Renal cell carcinoma (RCC) is among the ten most frequently diagnosed cancers worldwide with male predominance and increased incidence in the older population. Metastatic disease is present in ~30% of clear cell RCC (ccRCC), the most common subtype of sporadic RCC, and correlates with poor prognosis, despite the use of targeted therapies. Primary ccRCC tumors are characterized by the loss of chromosome 3p, resulting in loss of heterozygosity of e.g. the tumor suppressor gene *VHL*, as well as by somatic mutations in driver genes such as *PBRM1*, *SETD2* and *BAP1*. In the present study, our aim was to elucidate the genetic landscape of distant RCC metastases derived from different organs, because data on the genetic variation of RCC metastases are currently limited.
Methods:
We investigated 79 distant metastases samples derived from 55 patients. 19 patients showed multiple metastases in the same organ or metastases in two or more different organs. The investigated metastatic tissues included paraffin embedded (FFPE) samples originated from 14 different organs among them metastases from lung (n=17), lymph nodes (n=14), adrenal gland (n=8) and liver (n=6). Comprehensive genetic analysis was performed through next generation sequencing (NGS) using a newly established gene panel targeting whole exon regions or selected gene regions of 33 different genes with a mean coverage of 1000x. These genes are already known to play an important role in the development and progression of RCC. For subsequent analyses only SNVs and small Indels were considered and correlated with clinical data of the patients.
Results:
In our cohort, *VHL* and *BAP1* were among the most frequently mutated genes overall in distant metastases whereas *HRAS* and *CTNNB1* were highly mutated only in specific organs. Analysis of different metastases of one patient highlights potentially clonal mutations. Shared variants in metastases of one patient were often classified as potentially damaging by various prediction tools. In addition, recurrent metastases before or after new courses of therapy, show higher mutational burden compared to earlier ones.
Discussion:
In summary, our data provide a first insight into the genetic landscape of ccRCC metastases, with implications on prognosis and therapy. The identified patient-specific somatic variants before and during RCC therapy can illustrate the development of metastasis in individual cases and thereby give information about the general evolution of metastases in RCC.

"PharmaNAGEN": Implementation of Pharmacogenomics in the Clinical Routines of the Public Health System Based on Next Generation Sequencing

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 103

Dr. Juan José Beloqui-Lizaso [1], Dr. Oscar Teijido [2], Ms. Luna Delgado de Mora [2], Mr. Alberto Maillo [3], Dr. Miren Vicuña Arregui [4], Dr. David Gomez-Cabrero [3], Dr. Angel Alonso-Sanchez [5]

1. *Genomic Medicine Unit, Navarrabiomed, Pharmacy Department Hospital Complex of Navarra (CHN)-Public University of Navarra (UPNA), Pamplona,* ***2.*** *Genomic Medicine Unit, Navarrabiomed, Hospital Complex of Navarra (CHN)-Public University of Navarra (UPNA), Pamplona,* ***3.*** *Translational Bioinformatics Unit, Navarrabiomed, Hospital Complex of Navarra (CHN)-Public University of Navarra (UPNA), Pamplona,* ***4.*** *Gastroenterology Department, Hospital Complex of Navarra (CHN), Pamplona,* ***5.*** *Genomic Medicine Unit, Navarrabiomed, Department of Medical Genetics, Hospital Complex of Navarra (CHN), Public University of Navarra (UPNA), Pamplona*

INTRODUCTION

One of the main challenges of Personalized Medicine relies on the individual variability of drug response and toxicity which significantly depends on gene variations associated with pharmacokynetics and pharmacodynamics. Pharmacogenetic strategies allow the selection of treatments according to the individual genetic profiles, which efficiently improves drug efficacy and safety with the subsequent minimization of costs. Current approaches based on unique gene-drug pairs provide, at best, only partial information of the individual pharmacogenetic profile. However, recent studies using whole genome sequencing estimate that most individual genomic profiles are worth for a guided prescription of at least one drug.

The aim of our pilot project, "PharmaNAGEN", is to promote the implementation of pharmacogenetics to the prescription routines of the Public Health System of Navarra (Spain). This strategy will rely on Whole Exome Sequencing (WES) from candidate patients and promoting the integration of the individual pharmacogenomic profile into the Clinical Decision Support System of the Public Health System creating a system of prescription alerts.

METHODS

This ongoing project attempts to recruit 450-500 patients diagnosed with inflammatory bowel disease (IBD), previously monitored for thiopurine methyltransferase (TPMT) activity and treated with thiopurine derivatives (azathioprine). After a genetic counseling session patients sign written informed consent forms approved by the Ethical Committee of Clinical Research of Navarra, in line with the ethical code of the World Medical Association (Declaration of Helsinki). DNA is extracted from peripheral blood or saliva and submitted to WES at the National Center of Genomic Analysis (CNAG), generating paired-end libraries using Nextera DNA Exome Kit (Illumina®) on the NextSeq 550 System (Illumina®) platform. High capacity storing facility (NASERTIC) stores and allows the access of data obtained from WES which is processed by bioinformatic analysis using reference genome GRCh38. We analyze genes directly linked to the metabolism of thiopurines as well as all the PharmGKB classified 1A-1B variant-drug combinations. Pharmacogenomic findings will be stored and aligned with a previously defined database containing the most relevant clinical recommendations associated with defined genotypes. This will create an automatic prescription alerts when required according to the pharmacogenetic profile of the patient.

RESULTS

We present data from the first 72 recruited patients and 18 pharmacogenes. As expected, all patients display heterogeneous pharmacogenetic landscapes (Figure 1), susceptible of alerts in the prescription system. Near 10% of individuals are genetically defective for TPMT activity which would increase the risk of side effects when treated with thiopurine derivatives. Among this subgroup, 80% of individuals are defective or ultrarapid metabolizers for other relevant pharmacogenetic routes.

DISCUSSION

Our preliminary results illustrate that WES provides wider and more accurate information of individual pharmacogenomic profiles. Using the combination of this approach together with development of an intelligent database conferring alerts to the prescription based on the pharmacogenetic profile, “PharmaNAGEN” attempts to provide a pioneer strategy of implementation of personalized treatments based on pharmacogenetic alerts in the Public Health Systems nationally and internationally.

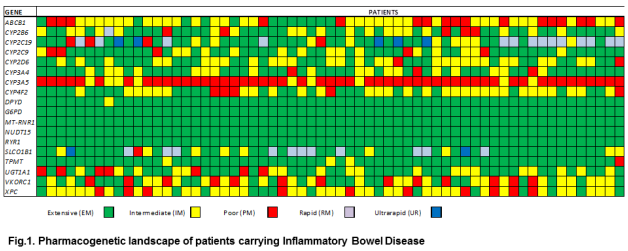

Fig.1. Pharmacogenetic landscape of patients carrying Inflammatory Bowel Disease

Figure 1. pharmacogenetic landscape of patients carrying inflammatory bowel disease.png

Structural racism in precision medicine: all patients are equal but some are more equal than others

Wednesday, 19th February - 13:15: Poster Presentation (Main Hall) - Poster - Abstract ID: 4

Mr. Lester Geneviève [1], ***Mr. Andrea Martani*** [1], ***Dr. David Shaw*** [2], ***Prof. Bernice Simone Elger*** [3], ***Dr. Tenzin Wangmo*** [1]

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Introduction

Precision medicine (PM) is an evolutionary approach to medicine and individualized care. Patients receive timely and tailored interventions based on their individual needs, the molecular taxonomy of diseases and hence their susceptibility profile to these diseases. One proposed aspect of such evolutionary approach is the convergence of three concepts, namely PM, learning healthcare systems and implementation science. By promoting the sharing of good quality health data and implementation of learning healthcare systems, physicians can address more precisely the needs of their patients. However, there are concerns that PM may also increase healthcare inequalities between racial and ethnic groups, due to its susceptibility to structural racism and its effects on the quality of health data collected on minority groups. Therefore, raising awareness on the potential and insidious impacts of structural racism is crucial to the promotion and safeguard of racial and social justice, a promise yet to be fulfilled by PM.

Methods

Three nodes along the process flow of the PM ecosystem, which are susceptible to the influences of structural racism, are analyzed. The first node concerns the collection of data from minority groups during their encounter with healthcare providers and researchers of the majority group, leading to bias in the health data sets. The second node depicts how bias in these health data sets can corrupt algorithmic decisions in artificial intelligence tools, which are increasingly used in the healthcare and research domains, leading to biased interpretation and more racial discrimination due to additional synergistic effects of deeply rooted implicit racial bias. The third node concerns how deliverables of PM initiatives might be corrupted by structural racism in healthcare and research domains (e.g. drug development and access to healthcare services).

Results

Specific challenges are identified and it is concluded that bias introduced in the health data sets will have cascading effects on the health of minority groups, leading to more racial discrimination imposed by the iterative nature of such convergence framework. Subsequently, specific actions to the three analyzed nodes are formulated to ensure that the insidious impact of structural racism on the quality of health data sets collected on minority groups are mitigated in PM initiatives. These actions include implicit bias training, increasing representativeness of ethnic minorities in healthcare professions, algorithmic impact assessments, and community-based research to name a few.

Discussion

Structural racism has shaped the working of our healthcare and research institutions for hundreds of years and it would be presumptuous to believe that PM initiatives will be safeguarded from its negative impact. Since health data sets are the basis of PM initiatives, it is paramount to safeguard their quality for minority groups, whose specific health problems and issues related to access to healthcare have often been neglected. To uphold the promise of personalizing care and promoting patients welfare regardless of ethnicity, PM initiatives therefore need to adopt the necessary actions to reduce the impact of structural racism.

Implementation of pharmacogenomics in Clinical Practice

Wednesday, 19th February - 14:10: Plenary Speeches: Pharmacogenomics and Precision Medicine (Auditorium) - Plenary Speech - Abstract ID: 129

Prof. Henk Jan Guchelaar [1]

1. *Leiden University Medical Center, Leiden*

Pharmacogenomics is the study of genetic variability affecting an individual's response to a drug. Its use allows personalized medicine and reduction in 'trial and error' prescribing, leading to more efficacious, safer and cost-effective drug therapy. Technical developments have moved the field from reactive genotyping to a pre-emptive panel approach: in this latter approach, patients are tested for a panel of genetic variants even before drug prescribing has taken place. When these data are included in a patient's electronic medical record, this allows physicians and pharmacists to use this information at the time of drug prescribing and medication surveillance. Due to its highly developed infrastructure, The Netherlands healthcare system is at the forefront of implementing pharmacogenomics into routine clinical practice. Pre-emptive testing of f.e. *DPYD* before the use of 5-fluorouracil or capecitabine and of *TPMT* before the use of 6-mercaptopurine or azathioprine is standard in many centers in The Netherlands and patient's drug dosages are personalized based upon the pharmacogenomics test result. In this presentation, an overview will be given of several pharmacogenomics implementation programs both in primary care and hospital care.

Recently, an EU Horizon2020 project Ubiquitous Pharmacogenomics (U-PGx) was funded and investigates the approach of pre-emptive panel testing using a randomized clinical trial design in 7 EU countries and including a total of 8,100 patients. Feasibility, health outcome, especially the reduction of adverse drug events, and cost-effectiveness will be studied. The U-PGx consortium ultimately aims to formulate European strategies for further improving the implementation of pharmacogenomics.

Pharmacogenomics and drug-induced liver injury

Wednesday, 19th February - 14:40: Plenary Speeches: Pharmacogenomics and Precision Medicine (Auditorium) - Plenary Speech - Abstract ID: 131

Prof. Ann Daly Newcastle [1]

1. *Newcastle University*

Hepatotoxic reactions to prescribed drugs (drug-induced liver injury or DILI) are a common cause of attrition in drug development programmes. Some types of DILI such as that induced by paracetamol overdose are concentration-dependent but other forms are idiosyncratic with patients developing symptoms of toxicity despite taking the causative drug at the recommended dose. Genetic factors predicting risk of idiosyncratic DILI have been studied extensively. Originally, these studies focussed on genes relevant to drug disposition and oxidative stress but since DILI patients sometimes show symptoms of immune-related toxicity in addition to liver enzyme elevation, studies on a HLA gene contribution were also performed. Two studies reported that the HLA allele DRB1*15:01 was a risk factor for DILI due to the antimicrobial co-amoxiclav. These convincing reports were followed by genome-wide association studies (GWAS) which demonstrated HLA associations for DILI due to a number of drugs, most notably flucloxacillin DILI where carriage of HLA-B*57:01 increases DILI risk approx. 80-fold. Despite the fact that B*57:01 is also a risk factor for development of abacavir hypersensitivity, underlying mechanisms for the flucloxacillin and abacavir toxicities appear different. The B*57:01-flucloxacillin DILI association is not sufficiently predictive of risk to currently justify preprescription genotyping but it may be possible to develop risk algorithms which also include other patient-specific factors. For co-amoxiclav DILI, GWAS showed that in addition to the DRB1*15:01 association, the HLA allele A*02:01 is also a risk factor and there is increasing evidence that non-HLA immunogenetic risk factors, particularly PTPN22 genotype, also contribute to overall risk. HLA genotype is not a risk factor for all forms of DILI. For drugs such as isoniazid and diclofenac, genetic factors relevant to drug disposition appear more important predictors of DILI susceptibility with no HLA association seen.

Pharmacogenomics and Psychiatric Disorders

Wednesday, 19th February - 15:10: Plenary Speeches: Pharmacogenomics and Precision Medicine (Auditorium) - Plenary Speech - Abstract ID: 133

Prof. Elvira Bramon [1]

1. *University College London*

Coming soon

Pharmacogenomics of thiopurine toxicity: make the case for precision medicine

Wednesday, 19th February - 15:40: Plenary Speeches: Pharmacogenomics and Precision Medicine (Auditorium) - Plenary Speech - Abstract ID: 124

Dr. Jun J. Yang [1]

1. *St. Jude Children's Research Hospital*

Elucidation of the genetic basis for inter-patient variability in drug toxicity not only reveals important biology of a drug's mechanism of action but also provides critical knowledge that enables risk-adapted treatment individualization. Thiopurines are widely used as anti-cancer drugs and as immunosuppressive agents, but also have a narrow therapeutic index due to hematopoietic toxicities. Therefore, there is a compelling rationale for improvements in evidence-based precision medicine approaches to maximize thiopurine efficacy while reducing side effects. By pharmacogenomic profiling, we comprehensively identify genetic factors associated with thiopurine toxicity with the goal to use this information to develop genetics-guided treatment individualization. For example, inherited deficiency in detoxification enzymes TPMT and NUDT15 predisposes children with leukemia to severe thiopurine-induced myelosuppression, and we show that preemptive dose adjustment based on gene genotype effectively minimizes host toxicity without compromising anti-cancer efficacy of this class of drugs. At the forefront of precision medicine, pharmacogenomics holds particularly great promise to transform medical practice with more efficacious and safer therapies across diseases.

Raman-laser-trapping: a novel analytical tool in personalized medicine

Wednesday, 19th February - 16:30: Oral Session: Personalized therapies (cancer, immunology, infectious diseases, clinical case studies, etc.) (Auditorium) - Oral - Abstract ID: 117

Dr. Hesham Yosef [1], ***Dr. Christian Klopsch*** [2], ***Dr. Daniela Marino*** [3], ***Dr. Karin Schuetze*** [1]

1. *CellTool GmbH,* ***2.*** *Department of Cardiac Surgery, Reference- and Translation Centre for Cardiac Stem Cell Therapy, University of Rostock,* ***3.*** *CUTISS AG*

Raman Trapping Microscopy (RTM) has emerged as a sensitive analytical tool in biomedical applications. It is a label-free and non-destructive microscopic technique that can examine live cells without inducing any cellular stress. The collected Raman results provide a biochemical fingerprint of the analyzed cell, which can be used to monitor induced-subcellular changes and track response to stimuli and therapeutic agents. Moreover, Raman results can provide valuable structural information about the bio-macromolecules in the cells such as proteins, lipids, nucleic acids, and carbohydrates. Recent developments of laser trapping have facilitated the Raman measurements of motile cells, bacteria, and extracellular vesicles in solutions, allowing direct measurements of liquid biopsies.

To demonstrate this strong potential of Raman in personalized medicine, we have implemented RTM in many cell therapy applications such as monitoring the differentiation of human mesenchymal stem cells (MSCs) derived from bone marrow to fibroblasts with great accuracy. RTM was also employed to detect the quality of therapeutic cell products such as *denovo* skin grafts, which is used as a skin-replacement in case of severe trauma or burn. In this application skin cells (Keratinocytes and fibroblasts) are collected from patients, expanded in 2D cultures and then seeded in separate layers on a 3D scaffold to form the skin graft. An important quality aspect is to check the cross-contamination between the keratinocytes and fibroblasts layers, which may compromise the integrity of the product. Current analytical standards for such products are expensive and destroy part of the graft. In contrast to these techniques, RTM can detect cross-contamination in the 2D and 3D cultures in a label-free, cost-effective, and non-destructive manner. Furthermore, RTM is showing promising potential in bacteria identification. Each bacteria species exhibits a characteristic Raman pattern that can be used to identify the species in body fluids. Implementing microfilters and microchannel chips can facilitate the separation of bacteria from blood, which can be directly measured and recognized by RTM. This is a promising approach to detecting sepsis. These previous examples highlight the great sensitivity and potential of Raman trapping microscopy in personalized medicine.

Patient-derived colon circulating cancer cells short term expanded in vitro for therapeutic screening

Wednesday, 19th February - 16:50: Oral Session: Personalized therapies (cancer, immunology, infectious diseases, clinical case studies, etc.) (Auditorium) - Oral - Abstract ID: 100

Prof. Natalia Malara [1], ***Dr. Angela Torsello*** [2], ***Dr. Franco Fulciniti*** [3], ***Dr. Ivan Presta*** [4], ***Dr. Anna Maria Lavecchia*** [5], ***Prof. Chiara Mignogna*** [5], ***Prof. Giuseppe Donato*** [4]

1. *University Magna Graecia,* ***2.*** *San Giovanni-Addolorata Hospital, Rome, Italy,* ***3.*** *Istituto Cantonale di Patologia, Locarno,* ***4.*** *University of Magna Graecia, Catanzaro, Italy.,* ***5.*** *Pugliese Hospital, Catanzaro, Italy*

IntroductionCarcinomas show remarkable genetic and phenotypic heterogeneity across individuals, leading to on demand personalised medicine. Here, we report in vitro cell expansion of circulating cancer cells from 24 patient blood samples of adenocarcinomas of colon and non-neoplastic epithelial circulating cells from blood-derived culture of individual 24 healthy samples. The blood-derived cultures of colon cancer patients, taken before anticancer treatments, recapitulate the cytological features of the primary tumours and maintain the genomic alterations of the original tumours during short-term expansion in vitro (≤14dys). Blood sampling was repeated after chemotherapy revealing the persistence of circulating cancer cells in 58% and change in mutational status in 29%, suggesting a new perspective of observation of the dynamic changes occurring during tumour progression through liquid biopsy circulating cancer cells assessment based.

Methods We conducted an observational prospective CHARACTEX (CHARActerization of Circulating Tumor cells and Expansion) project in patients with a cancer diagnosis and healthy subjects. Within 4 hours from blood sampling collection, the cells were isolated through a gradient passage and seeded, in chamber slide (figure 1) useful for cytological preparations, in plate (Figure 1) to test chemosensitivity and to obtain the pellet employed for the mutational analysis.

Results Blood sampling was repeated before and after chemotherapy in 24 patients revealing the persistence of circulating cancer cells in 14 patients with different grade of toxicological signatures due to the personalized responsivity to the drugs based therapy. In 7 of these patients, the primary mutational status changed in response to drugs based on their new genomic alterations: EGFR-mutant to erlotinib, and an EGFR-mutant/MET-amplified to crizotinib.

DiscussionConsidering the short time from primary circulating cell line establishment to drug testing, our newly developed model may prove useful for predicting patient-specific drug responsivity through ex vivo patient-specific drug trials.

References

Malara N, et al. Nature Precision Oncology 2, 26 (2018)

Malara N, et al Journal of Translational Medicine 14, 133 (2016)

Malara N. Small. Nov 12;10(21):4324-31. (2014)

Malara N. et al BMC Neurology 8, 16 (2016)

Figure 1. Representative cultures of circulating colon cancer cells from patient with localized (I and II stage of disease) and advanced disease (III-IV stage) performed on plate, characterized by adherent and spheroidal growth and on slide stained with Hematoxylin & Eosin at 0; 7 ; 14 days of observation.

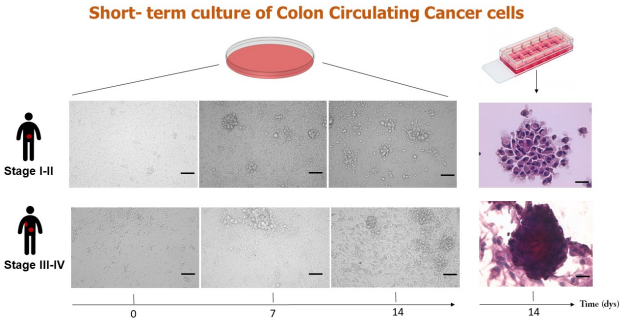
Short- term culture of Colon Circulating Cancer cells
Stage I-II
Stage III-IV
0
7
14
14
Time (dys)

Figura 1.jpg

An integrated bioinformatics pipeline for functional drug response profiling in pediatric precision oncology

Wednesday, 19th February - 17:10: Oral Session: Personalized therapies (cancer, immunology, infectious diseases, clinical case studies, etc.) (Auditorium) - Oral - Abstract ID: 55

Ms. Dina ElHarouni [1]***, Prof. Olaf Witt*** [2]***, Dr. Matthias Schlesner*** [1]***, Dr. Sina Oppermann*** [2]

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Introduction: High throughput drug screening platforms measuring the sensitivity of cell lines and primary patient cells to chemical perturbations on a large scale have been rapidly evolving and aim to integrate drug response profiles to genomic features. Through direct screening of patient-derived tumor cells, such platforms can be used to discover new predictors of drug response, thereby adding evidence for therapy decision making in precision medicine. We have established and implemented an ex-vivo drug response profiling platform for primary pediatric solid tumors within the INFORM (INdividualized Therapy FOr Relapsed Malignancies in Childhood) registry study, to complement the molecular profiles with functional drug sensitivity data, aiming to identify therapeutic targets and new treatment options for pediatric patients with relapsed or refractory high risk disease. Within this platform, vital tumor samples are screened using a library of 75 FDA approved drugs, each tested with 5 different concentrations in replicates using metabolic readouts in 384 well format (CellTiter Glo).

Methods: We developed a user-friendly bioinformatics pipeline to analyze and visualize high throughput drug screening data. The pipeline uses three state-of-the-art R packages: i) DrugScreenExplorer to conduct quality control and normalize readouts to positive and negative controls; ii) n-parameter logistic regression model to fit dose-response curves according to the best goodness of fit with the inclusion of proliferating drug response profiles; and iii) the Drug Sensitivity Score algorithm based on continuous modeling of drug response parameters to identify top hit sensitivity drugs. The complete workflow was implemented as interactive shiny app that can be used directly by biologists and clinicians to analyze drug screening experimental outputs and report top hit drugs for discussion in molecular tumor boards.
Results: Our pipeline allows for quality control conduction, automated screening analysis, hit scoring, and further integration of drug response data with the corresponding omics profiles of cell lines and patient samples. In addition, a quantitative differential drug sensitivity scoring specific to cancer cells can be calculated if a control sample is provided. Not only can the pipeline analyze any plate layout for single-agent drug libraries, but it can also be adapted for combination drug screens, identifying hit drug combination scores per patient sample. The
pipeline has been applied on five genetically defined pediatric 3D-tumour cell-lines with known vulnerabilities and molecular profiles for proof-of-concept. Top hit reported drugs matched the molecular characteristics of the tested cell-lines, i.e response to BRAF and MEK1/2 inhibition in a BRAFV600 mutated model, and sensitivity to Trk inhibitors of a model with NTRK fusion, demonstrating the predictive power of ex-vivo drug response profiling in pediatric oncology. For clinical translation, the pipeline was applied on 12 INFORM patient-derived pediatric solid tumors, successfully providing response profiles and top hit drug scores for discussion in the molecular tumor board.

Discussion: Our user-friendly pipeline allows interactive exploration of drug screening data in a graphical user interface. It provides a variety of functions to assist the identification of selective drugs from personalized drug

response profiles, and hence can help to bring drug response profiling to clinical practice.

Perfusion Air Culture of Tissue Slices to Predict Personalized Therapy Response of Solid Tumors

Wednesday, 19th February - 17:30: Oral Session: Personalized therapies (cancer, immunology, infectious diseases, clinical case studies, etc.) (Auditorium) - Oral - Abstract ID: 62

Ms. Kathrin Böpple [1], ***Dr. Meng Dong*** [1], ***Dr. Bernd Winkler*** [2], ***Dr. Emma Davies*** [3], ***Dr. Julia Schüler*** [4], ***Mr. Markus Kleih*** [1], ***Prof. Hans-Georg Kopp*** [5], ***Dr. Frank Essmann*** [1], ***Prof. Walter Aulitzky*** [6]

1. *Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart and Eberhard Karls University, Tuebingen,* ***2.*** *Robert-Bosch-Krankenhaus, Department of Gynaecology and Obstetrics, Stuttgart, Germany,* ***3.*** *Oncology iMed, Bioscience, AstraZeneca, Alderley Park, Macclesfield, SK10 4TG, United Kingdom,* ***4.*** *Charles River Discovery Research Services Germany GmbH, Am Flughafen 12-14, 79108 Freiburg, Germany,* ***5.*** *Robert-Bosch-Krankenhaus, Department of Molecular and Pneumological Oncology; Robert Bosch Center for Tumor Diseases (RBCT), Stuttgart, Germany,* ***6.*** *Robert-Bosch-Krankenhaus, Department of Internal Medicine, Oncology and Hematology, Stuttgart, Germany*

Both time and knowledge are crucial factors in anti-cancer therapy because the earlier an efficient therapy starts the higher are chances to eradicate a tumor in the patient's organism. Within individual patients it is impossible to test several drugs at the same time. Drug screenings with traditional 2D cell culture systems are often poorly translated into 3D *in vivo* situations. As a compromise, 3D organoids from patients have been suggested to be used for personalized medicine, but the extracellular matrix and non-tumor cells such as stroma cells and immune cells are missing from organoids. However, the (individual) tumor microenvironment (TME) created by the interplay of tumor and non-tumor cells is hard to model yet, the TME acceptably has a significant impact on therapy response. Therefore, we developed a predictive pre-clinical model for solid cancers to investigate tumor response for different drugs or drug combination that can be applied in parallel to tumor tissue slices (TTS) comprising the patient's TME. After 3 days the therapy response will be analyzed by immunohistochemistry and thereby support the physician's choice of medication.

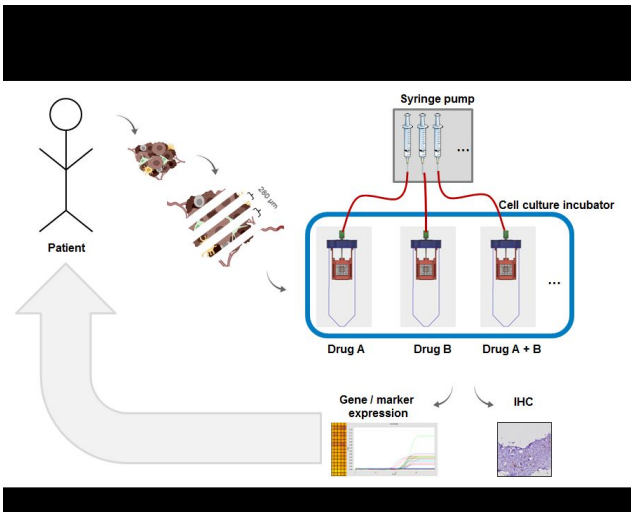
Commonly, TTS are cultured statically on a filter support at an air-liquid interface and this gives rise to intra-slice biomarker expression gradients. We overcame this problem with the newly developed perfusion air culture (PAC) system. In the PAC system TTS are kept in-between two organotypic supports and fixed in a frame holder. The tumor-slice-organotypic-support sandwich containing frame holder is held inside a 50 mL tube with air exchange capacity. Everything is placed in a conventional cell culture incubator. Cell culture media are supplied to the TTS from a syringe pump via a silicon tube. This allows continuous perfusion of medium and the drugs to be tested to each individual slices.

To validate the PAC system we used different cell line-derived xenografts and primary human ovarian carcinomas. Subsequent immunohistochemical analyses of biomarkers to study tumor morphology, cell proliferation, DNA damage and apoptosis of the TTS after culture. High-throughput RNA expression analysis of the tissue was conducted via chip-technology. Collected biomarker data were used to compare *ex vivo* control samples and TTS after PAC culture. Morphology and structure of the TTS slices before and after PAC culture were similar.

In pharmacological perturbation experiments the culture medium was supplemented with clinically relevant concentrations of Cisplatin, mimicking the *in vivo* situation in patients. TTS slices were constantly perfused for 72 h. As expected, Cisplatin perturbation leads to an increase of apoptotic marker expression.

We have established a pre-clinical model for *ex vivo* TTS culture with our novel PAC system. TTS can be cultivated for up to 7 days and pharmacological perturbation can be performed under precisely controlled conditions. The system closely resembles the *in vivo* situation by preserving the tumor microenvironment and is therefore suitable for individual testing of drug efficacy for personalized medicine.

This work is partially supported by the Robert Bosch Stiftung, Stuttgart, Germany.



Workflow.jpg

MiR-21 in cardiac macrophages controls cardiac fibrosis and determines pressure overload-induced cardiac dysfunction

Wednesday, 19th February - 17:50: Oral Session: Personalized therapies (cancer, immunology, infectious diseases, clinical case studies, etc.) (Auditorium) - Oral - Abstract ID: 61

Dr. Deepak Ramanujam [1], ***Ms. Anna Patricia Schön*** [1], ***Ms. Christina Beck*** [1], ***Dr. Giulia Felician*** [1], ***Dr. Anne Dueck*** [1], ***Prof. Stefan Engelhardt*** [1]

1. *Institut für Pharmakologie und Toxikologie, Technische Universität München, Munich, Germany*

Cardiac macrophages (cMPs) are increasingly recognized as important regulators of myocardial homeostasis and disease, yet the role of noncoding RNA in these cells is largely unknown. Small RNA sequencing of the entire miRnomes of the major cardiac cell fractions revealed microRNA-21 (miR-21) to account for the single highest expressed miR in cMPs in health and to further increase in disease (15 and 43% of all miR reads respectively). MiR-21 has been previously reported as a key microRNA driving tissue fibrosis. Here, we sought to determine the function of macrophage miR-21 on myocardial homeostasis and disease-associated remodeling and the effects of macrophage-specific manipulation on the latter.

Mice with macrophage-specific (Cx3cr1-Cre-mediated) genetic deletion of miR-21 were protected from interstitial fibrosis and cardiac dysfunction when subjected to pressure overload of the left ventricle. Single cell sequencing of pressure-overloaded hearts and analysis of RNA maturation kinetics revealed that deletion of miR-21 in macrophages favoured their polarization towards a M2-like, reparative phenotype. Systematic quantification of intercellular communication mediated by ligand-receptor interactions across all cell types revealed that miR-21 primarily determined macrophage-fibroblast communication, favouring transition of quiescent fibroblasts towards the myofibroblast phenotype. The differentiation of isolated macrophages in vitro towards a pro-inflammatory phenotype activated myofibroblast transdifferentiation of CF in a paracrine manner and was dependent on the rapid induction of miR-21 in MPs.

Taken together, our data indicate a critical role of cMPs in presssure overload-induced cardiac fibrosis and dysfunction and reveal macrophage miR-21 as a key molecule determining the pro-fibrotic role of cMPs.

Feasibility of integrating panel-based pharmacogenetics testing to guide the prescription of opioids.

Wednesday, 19th February - 16:30: Oral Session: Integrating Big Data (Break-Out Room) - Oral - Abstract ID: 8

Dr. jean-christophe boyer [1], ***Dr. olivier bredeau*** [2], ***Dr. francois jedryka*** [2], ***Dr. nathalie maignaut*** [2], ***Prof. eric viel*** [2]

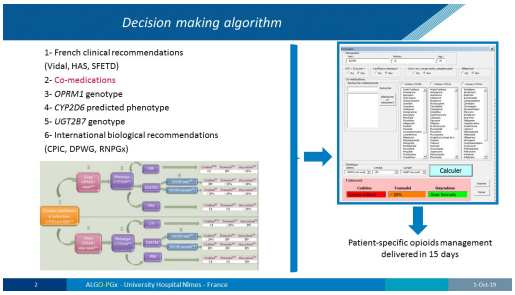
1. *Nimes university hospital,* ***2.*** *pain evaluation and management center, university hospital nîmes*

Inappropriate opioids prescribing increases patient illness owing to adverse drug events. Our aim was to assess the feasibility of implementing next generation sequencing (NGS) to guide the prescription of three main opioids namely, codeine, tramadol and oxycodone into clinical practice, in real-time, for patients with respect to chronic non cancerous pain.

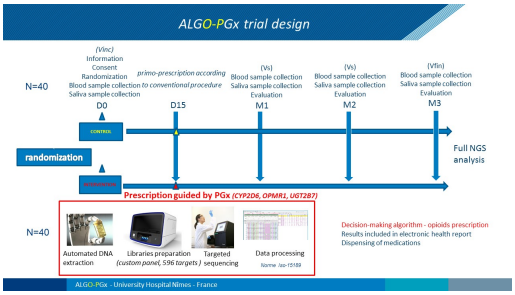
Methods: ALGO-PGx, a pilot randomized controlled trial that compared pharmacogenetic-guided treatment strategy (n=40) to usual care (n=40) was established (NCT03498014).

Results: NGS workflow was based on a custom capture panel (Nextera Flex for enrichment, Illumina) for sequencing CYP2D6 locus, UGT2B7 and OPMR1variants among the 596 targets covering 54 genes (182 kb) included in the panel and related to 8 therapeutic domains. A decision-making algorithm was developed from recent literature and from a joint reflection between clinicians and biologists, taking into account genetic, pharmacokinetic and pharmacodynamic criteria. It is based on the pharmacogenetics status of the patient and on the other associated medications being used. The software supporting the algorithm allows choosing the best treatment among the three opioids studied, and to accurately determine the best dosing recommendations.

Discussion: At the time of this abstract submission, this pre-emptive approach will be used in the ALGO-PGx trial starting on November 2019. This presentation will focus on lessons learned through our attempts of clinically implementing PGx testing, linked to several technical and clinical limitations and administrative barriers.



Algorithm.jpg



Design of algo-pgx.jpg

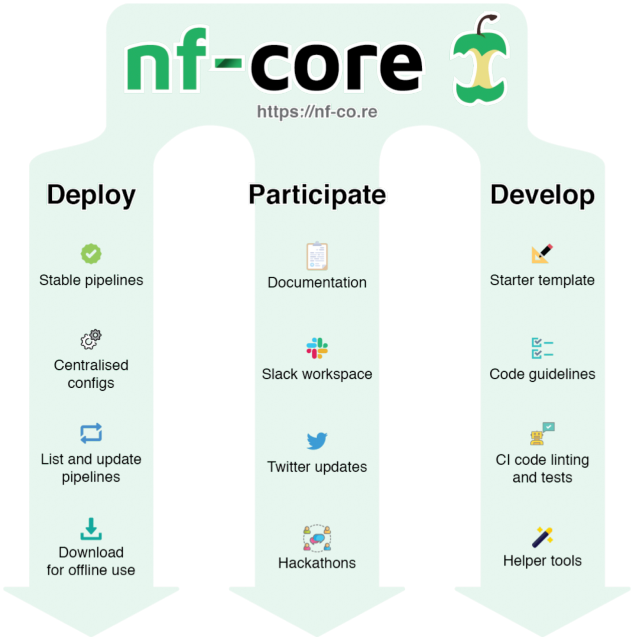
FAIRification of data and software in precision medicine using nf-core

Wednesday, 19th February - 16:50: Oral Session: Integrating Big Data (Break-Out Room) - Oral - Abstract ID: 98

Dr. Sven Nahnsen [1]

1. *Quantitative Biology Center (QBiC), University of Tübingen*

Introduction:
The standardization, portability, and reproducibility of analysis pipelines is a renowned problem within the general bioinformatics community and it is of particular importance when data-driven processes are moving towards patient care. Data processing pipelines are often designed for execution on-premise, and this inevitably leads to a level of customisation and integration that is only applicable to the local infrastructure, yet, precision medicine needs to integrate many remote data sources and infrastructures. We introduce *nf-core*, a framework that provides a community-driven platform for the creation and development of best practice analysis pipelines.
Methods:
Based on nextflow, it comes with built-in support for pipeline execution on most computational infrastructures, as well as automated deployment using container technologies such as Conda, Docker, and Singularity. Therefore, key obstacles in pipeline development such as portability, reproducibility, scalability and unified parallelism are inherently addressed by all *nf-core* pipelines. Furthermore, to ensure that new pipelines can be added seamlessly, and existing pipelines are able to inherit up-to-date functionality the *nf-core* community is actively developing a suite of tools that automate pipeline creation, testing, deployment and synchronization. The peer-review process during pipeline development ensures that best practices and common usage patterns are imposed and therefore, adhere to community guidelines.
Results and Discussion:
With nf-core we provide a community-driven platform for high-quality, excellent documented and reproducible bioinformatics pipelines. We have also developed a suite of tools that assist in the creation and development of both new and existing pipelines. Our primary goal is to provide a platform for high-quality, reproducible bioinformatics pipelines that can be utilized across various institutions and research facilities. All together, with nf-core we build the basis FAIR (Findable, Accessible, Interoperable and Reusable) software and data and their translational use in data-driven precision medicine.



2020-01-13 nf-core.png

Integration of Polygenic Risk Score in Coronary Artery Disease risk models for clinical use

Wednesday, 19th February - 17:10: Oral Session: Integrating Big Data (Break-Out Room) - Oral - Abstract ID: 110

Dr. Giordano Bottà [1], ***Dr. Alessandro Bolli*** [1], ***Mr. Paolo Di Domenico*** [1]

1. *Allelica*

Introduction

Polygenic Risk score (PRS) is a powerful tool for identifying individuals at high genetic risk of developing complex diseases. PRS aggregates the genetic contribution of several genetic variants, each one with a small effect, but when combined they are able to increase the risk at a clinically-actionable level. In the last two years, new genome-wide PRSs for Coronary Artery Disease (CAD) have been developed, showing promising results for clinical applications. Although PRSs demonstrated higher predictive performance than any currently used risk factor, they are not applied in clinical practice and their integration in clinical absolute risk models was not yet explored.

Methods

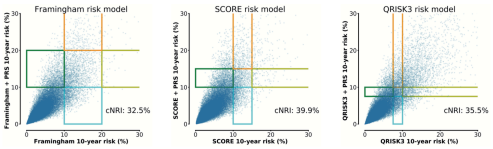
We used the largest prospective genotyped cohort available to date, the UK Biobank, and a recently developed algorithm called SCT, to develop a new PRS for CAD. The interim release of UK Biobank was used as validation dataset. We tested the predictive performance of the new CAD PRS, along with the already published PRSs from (Khera et al. 2018) and (Inouye et al. 2018), in the second release of the UK Biobank used as testing dataset. Individual CAD PRS was used as predictive variable in a logistic regression model, with additional covariates such as age, gender, genotyping array, and the first 4 principal components of ancestry. Clinical data comprising the risk factors of Framingham, QRISK3, and SCORE risk models have been collected for each individual of the testing dataset. To quantify associations between clinical risk factors and CAD incident outcomes, Hazard Ratios were calculated using Cox proportional hazards models. For each individual, the 10-year absolute risk of developing CAD was calculated according to Framingham, QRISK3, and SCORE risk models with and without PRS integration.

Results

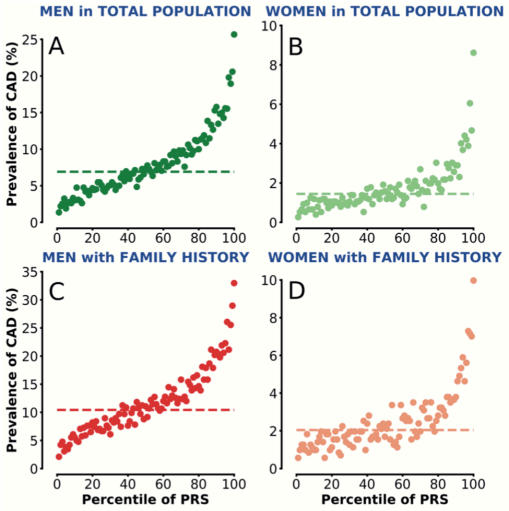
The new PRS for CAD (SCT-I) demonstrated better predictive performance than previously published CAD PRS (AUC improvement: 0,005). The addition of PRS to current clinical risk models improves their predictive performances (Framingham AUC improvement: 0,02, SCORE AUC improvement: 0,03, QRISK3 AUC improvement: 0,02) and determines a reclassification of individuals among risk categories, with a Net Reclassification Improvement (cNRI) ranging from 32.5% to 40%. PRS-induced risk reclassification showed implications in a primary care scenario: if individuals at intermediate risk are targeted for PRS screening and treated with statins if necessary according to current risk guidelines, one extra CAD outcome could be prevented for every 239 (Framingham), 202 (SCORE), and 145 (QRISK3) individuals screened.

Discussion

These results suggest that the targeted assessment of PRS for individuals at intermediate risk would have a deep impact in a public health scenario, increasing the number of CAD cases that will be prevented and thus reducing the cost associated with healthcare intervention.



Prs integration in clinical risk models.png



Prs risk stratification.png

Best Practice: Achieving Personalised Medication for Everyone

Wednesday, 19th February - 17:30: Oral Session: Integrating Big Data (Break-Out Room) - Oral - Abstract ID: 102

Mrs. Herna Muñoz-Galeano [1]

1. *HMG Systems Engineering GmbH*

PGXperts Platform helps doctors manage complex medication for individual patients in a safe and easy way. Medication risk is due not only to individual genetic make-up, but also because of interactions between drugs, drugs and food as well as lifestyle. In one single integrated solution it is possible for the physician to significantly reduce medication risks by considering all these aspects. This is true particulary for polypharmacy patients.
PGXperts Platform, developed by HMG Systems Engineering (HMG), follows an intuitive and seamless process, to stratify risks. The first step is to identify interaction risks of any drug cocktail, in less than one minute, using the PGXperts InteractionsCheck. In case there is risk of drug-gene interactions, it leads to a pharmacogenetic test for the respective patient. As a result the physician will recieve a comprehensive and actionable report, the PGXperts PerforM. It allows him to prescribe a **personalised medication** with minimal risk. The patient will receive the pharmacogenetic profile - PGxProfil. This decision support process has been designed together with physicians to optimise treatment outcomes and for health cost efficacy. It follows the principles of personalised medication and reduces risk of adverse treatment.
With the PGXperts platform we deliver validated, evidence based and actionable results, adhering to highest quality standards. Our curated database is cross-referenced with local and international pharmacogenetics societies. Our in-house team of researchers and quality controllers continuously foster the growth of an industry-unique database containing information of more than 48.000 drugs and substances, 173 gene variations and 60 diets and herbs. The in-house curation of this database significantly reduces complexity of end-to-end processes and risk for patients with challenging medication plans.

The PGXperts platform is based on the combined knowledge of a unique range of innovators from the fields of state-of-the-art software engineering, UX-design, molecular biology, pharmacogenetics, medical practice, data science and platform development. The innovative power of the platform is designed to manage medication complexity, deliver ultra-fast results and an accommodating user experience. The technology is device-agnostic and adheres to local and international data security standards.
HMG has been awarded with several innovation prizes for its activities: IHK-Gründerpreis Mittelfranken 2019 | TOP 100 of the most innovative SMEs in Germany 2016 | 2nd Price PerMediCon-Award 2016.

Personalized medicine awareness and attitude among undergraduate medical students at Tanta University

Wednesday, 19th February - 17:50: Oral Session: Integrating Big Data (Break-Out Room) - Video - Abstract ID: 128

Dr. Abdelazeem Elhabyan [1], ***Prof. Ibrahim Kabbash*** [1], ***Dr. Mohamed Khaled*** [1], ***Dr. Kareem Waheed*** [1], ***Dr. Gehad Moussa*** [1], ***Dr. Eslam Hashish*** [1], ***Dr. Abdullah Masri*** [1], ***Dr. Mahmoud Halimeh*** [1], ***Dr. Abdelrahman Eltonoby*** [1], ***Dr. Alshymaa Attia*** [1], ***Dr. Mohamed Hindawi*** [1]

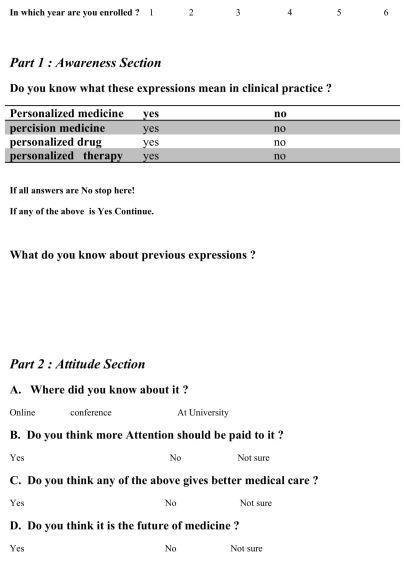
1. *Tanta University , Faculty of Medicine*

Introduction:
There is rapid progress in genome sequencing technologies that lead to the concept of personalized medicine, in which we use genomics to direct health care.
Few studies measure the awareness and attitude of personalized medicine among undergraduate medical students. Moreover, the sample size is not big enough to measure the level of awareness accurately in each medical year separately. Hence; we conducted this study to cover previous defects.
Methods:
A cross-sectional study using a questionnaire that we designed to measure the awareness and attitude towards personalized medicine in all 6 years of medical education.
The least sample size accepted was calculated using Epi-info program version3.01 with a 95% confidence level and margin of error of 5% for each year separately. The Total sample size was 1497students**.**
The Questionnaire-attached below Figure.1-consisted of 2 sections: the first one was an awareness section designed to measure awareness of students by yes or no questions and to confirm their answers, we added an open-ended question (what do you know about it ?). This divided participants into 3 categories as in the results below (table 1).
The second section was designed for those who knew the meaning of personalized medicine concepts to check their attitude towards it. (table 2)
Results:
Participants belonged to one of three categories: **82.6%** of students did not know anything about personalized medicine, **14.5%** had a misconception, and only **2.87%** knew what personalized medicine is.***Chi-square*****= 6.603, p = 0.010** (knew one or more expression versus the other two categories). **Overall**, the attitude of those who knew the concept -2.87%- was that we should pay more attention to personalized medicine because is it the future of medicine.
Discussion:
A minority of students knew about it personalized medicine (2.87%)
This is a very low level of awareness compared with other studies but can be explained by the wider use and applications of personalized medicine in Europe and the U.S.

Level of awareness attains its lowest level in the 6th year and this should be addressed as they are the future doctors, they will deal with patients in a year.

There is a large number of students with a misconception that needs to be corrected using all resources as university lectures, workshops, scientific meetings, and online courses. This misconception was not addressed by previous studies, so we addressed it using the open-ended questions(What do you know about personalized medicine?).

The **2.87%** who knew the concept had different sources for their knowledge: 55.81% of them knew about personalized medicine through the internet, while the other half (41.86%) knew about it in Tanta university. Accordingly, the university rule should be reevaluated.
The majority of the 2.87%, who knew the concept, thought that more attention should be paid to personalized medicine and that reflects their feeling that the issue is not well covered as needed. Additionally, they thought that it gives better medical care, and it is the future of medicine. This is a more positive attitude compared to previous studies.



In which year are you enrolled ? 1 2 3 4 5 6

Part 1 : Awareness Section

Do you know what these expressions mean in clinical practice ?

Personalized medicine	**yes**	**no**
percision medicine	yes	no
personalized drug	yes	no
personalized therapy	yes	no

If all answers are No stop here!

If any of the above is Yes Continue.

What do you know about previous expressions ?

Part 2 : Attitude Section

A. Where did you know about it ?

Online conference At University

B. Do you think more Attention should be paid to it ?

Yes No Not sure

C. Do you think any of the above gives better medical care ?

Yes No Not sure

D. Do you think it is the future of medicine ?

Yes No Not sure

Figure1-study tool questionaire - part 1 was answered by all paritcipatns while part 2 was answered by only those who knew at least 1 expression of personalized medicine.jpg

Table.1 explains the level of awareness of different expressions of personalized medicine (i.e. personalized medicine, precision medicine, personalized drug, and personalized therapy) among different medical years.

Medical year	*Did not know any expression of personalized medicine*		*Misconception of personalized medicine*		*Knew one or more expression of personalized medicine*	
	n	%	n	%	n	%
1st year N=229	132	57.6	79	34.5	18	7.9
2nd year N=289	253	87.5	34	11.7	2	0.7
3rd year N=267	224	83.9	36	13.5	7	2.6
4th year N=260	232	89.2	23	8.9	5	1.9
5th year N=247	224	90.7	13	5.3	10	4.1
6th year N=205	172	83.9	32	15.6	1	0.5
Total N=1497	**1237**	**82.6%**	**217**	**14.5%**	**43**	**2.9%**

$X^2 = 6.603$, p = 0.010(comparing different medical years)

Table1-different categories of participants according to their awareness with personalized medicine.jpg

Table.2 includes answers to questions in the second part of the questionnaire that were only answered by those who knew one or more expressions of personalized medicine (2.9% N=43)

Question	Number	%
Which term is more common?		
Personalized medicine	42	96.7%
Precision medicine	25	58.1%
Personalized drug	40	93%
Personalized therapy	37	86.1%
Where did they knew about it?		
Online	24	55.8%
University curriculum	18	41.9%
Conference attendance	1	2.3%
Do you think more attention should be paid to it?		
Yes	38	88.4%
No	1	2.3%
Not sure	4	9.3%
Do you think it gives better medical care?		
Yes	40	93.1%
No	1	2.3%
Not sure	2	4.7%
Do you think it is the future of medicine?		
Yes	35	81.4%
No	2	4.7%
Not sure	6	13.9%

Table 2 - analysis of answers to questions in the second part of questionaire . these questions were answered only by those who knew at least one expression of personalized medicine correctly.jpg

Precision Medicine and Breast Cancer

Thursday, 20th February - 09:00: Plenary Speeches: Oncology (Auditorium) - Plenary Speech - Abstract ID: 134

Prof. Douglas Easton [1]

1. *University of Cambridge*

Coming soon

Aggressive Lymphomas: The Road to Precision Medicine

Thursday, 20th February - 09:30: Plenary Speeches: Oncology (Auditorium) - Plenary Speech - Abstract ID: 142

Prof. German Ott [1]

1. *Robert-Bosch-Krankenhaus, Department of Clinical Pathology, Stuttgart, Germany*

Coming soon

Chemokines as tools and targets for personalized cancer immunotherapy.

Thursday, 20th February - 10:45: Plenary Speeches: Innovation in Precision Medicine (Auditorium) - Plenary Speech - Abstract ID: 135

Prof. Stefan Endres [1]

1. *University Munich*

Coming soon

Single Cell Sequencing and Precision Medicine

Thursday, 20th February - 11:15: Plenary Speeches: Innovation in Precision Medicine (Auditorium) - Plenary Speech - Abstract ID: 20

Prof. Muzlifah Haniffa [1]

1. *Newcastle University*

Muzlifah has used functional genomics, comparative biology and more recently single cell RNA sequencing to study human mononuclear phagocytes. In this seminar, she will discuss the power and utility of single cell RNA sequencing to understand the functional organisation of the developing human immune system.

Ultra-rapid detection of high-order synergistic targeted drug combinations for personalized treatment of colorectal cancer

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 112

Mrs. Marloes Zoetemelk [1], Mr. George Ramzy [1], Ms. Magdalena Rausch [1], Dr. Thibaud Koesler [2], Dr. Judy R van Beijnum [3], Dr. Andrea Weiss [1], Mr. Valentin Mieville [1], Dr. Sander Piersma [4], Dr. Richard de Haas [4], Dr. Celine Delucinge-Vivier [5], Dr. Axel Andres [6], Prof. Christian Toso [6], Prof. Alexander Henneman [4], Dr. Myléne Docquier [5], Prof. Thomas McKee [7], Prof. Connie Jimenez [8], Prof. Youssef Daali [9], Prof. Arjan W. Griffioen [10], Prof. Laura Rubbia-Brandt [7], Prof. Pierre-Yves Dietrich [2], Prof. Patrycja Nowak-Sliwinska [1]

1. *Molecular Pharmacology Group, Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva,* ***2.*** *Department of Oncology, Geneva University Hospitals and Faculty of Medicine,* ***3.*** *Angiogenesis Laboratory, Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam UMC-location VUmc,* ***4.*** *OncoProteomics Laboratory, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit Amsterdam,* ***5.*** *iGE3 Genomics Platform, University of Geneva,* ***6.*** *Translational Department of Digestive and Transplant Surgery, Geneva University Hospitals and Faculty of Medicine, 7. Department of Genetic Medicine, Laboratory and Pathology, University Hospitals of Geneva (HUG),* ***8.*** *Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit Amsterdam,,* ***9.*** *Division of Clinical Pharmacology and Toxicology, Department of Anaesthesiology, Pharmacology, Intensive Care and Emergency Medicine, Geneva University Hospitals,* ***10.*** *Angiogenesis Laboratory, Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam UMC-location VUmc, VU University Amsterdam*

Personalized treatment targeted to genetics of a tumor has resulted in promising responses, however an unmet need for further improvement still remains. Colorectal carcinoma is clinically treated with chemotherapeutics, often supplemented with targeted agents. However, an urgent need exists for treatment improved long-term activity and reduction of side effects. Using our previously developed statistical approach termed therapeutically guided multidrug optimization (TGMO), in only few experimental steps, we identified optimal drug combinations (ODC). The ODC contained three to four synergistic targeted compounds administered at low doses. RNA sequencing and phosphoproteomics analyses indicated that multi-drug partial target inhibition resulted in subtle multi-node regulation of cell signaling. The mechanism of action of these ODCs mostly converged towards MAP kinase signaling and cell cycle arrest despite differential cell mutation status, transcript expression levels or protein kinase phosphorylation state. Selected cell-specific ODCs were subsequently translated to *in vivo* models, in which the ODCs reduced efficiently tumor growth and significantly outperformed standard chemotherapy combination. The drug combinations had unique pharmacokinetic profiles compared to single drugs with most notably enhanced drug bioavailability. Finally, the optimized ODCs were also active in freshly resected patient material. Overall, we proved that our TGMO technology guides towards selective and effective low-dose high order drug mixtures, with potential to improve CRC treatment.

Bringing the Algorithms to the Data - Distributed Medical Analytics using the Personal Health Train Paradigm

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 107

Mr. Marius Herr [1], ***Mr. Lukas Zimmermann*** [2], ***Prof. Nico Pfeifer*** [3], ***Prof. Oliver Kohlbacher*** [4]

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Introduction:
The 'Personal Health Train' (PHT, \ref{fig:train}) is a paradigm proposed within the GO-FAIR initiative as one solution for distributed analysis of medical data, enhancing their FAIRness. Rather than transferring data, the analysis algorithm (wrapped in a 'train'), travels between multiple sites (e.g., hospitals - so-called 'train stations') hosting the data in a secure fashion. Implementing trains as light-weight containers enables even complex data analysis workflows to travel between sites, for example, genomics pipelines or deep-learning algorithms - analytics methods that are not easily amenable to established distributed queries. We present a prototypical PHT implementation developed within the context of the German national medical informatics initiative and demonstrate how modern cloud techniques can be leveraged for complex distributed, privacy-preserving medical data analytics.
Methods:
The scope of applications of the infrastructure ranges from statistical queries to complex machine learning algorithms, or sophisticated omics and image analyses. Local software installation beyond the train station infrastructure is not required. To participate, a station only needs to deploy a lightweight platform application, which provides the communication interface with the registry. Currently, the train station provided access to local data repositories. Each constructed train image is immutable and thus enhances reproducibility of analyses. A comprehensive Python library has been developed that
facilitates the implementation of train images and minimises incurred overhead.

Results / Discussion:
At this stage, the Personal Health Train has successfully been deployed for
implementing use cases in the medical informatics initiative in Germany, such as counting patients with certain diagnoses in a hospital. Currently we are developing and implementing more advanced methods to allow a wide range of machine learning methods and genomic pipelines.

Single-platform metabolomic and proteomic profiling as innovative tool for comprehensive phenotyping of human tissue

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 52

Dr. Thierry Schmidlin [1], Dr. Kathrin Klein [1], Dr. Stefan Winter [1], Prof. Matthias Schwab [1], Dr. Thomas E. Mürdter [1], Dr. Ute Hofmann [1], Dr. Mathias Haag [1]

1. *Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology Stuttgart and Eberhard-Karls-University, Tuebingen*

Introduction

Merging tissue-derived proteomics and metabolomics data represents a promising strategy to gain insight into pathophysiological processes and to reveal functionally relevant metabolome-proteome relationships. This is in particular important for heterogeneous tumor material where more reliable data can be retrieved from a single piece of tissue rather than from replicate sample aliquots. Here we demonstrate a strategy for the quantitative assessment of metabolites and proteins derived from the very same liver tissue sample analyzed on the same analytical platform.

Methods

Human liver tissue samples derived from the IKP liver bank were sequentially subjected to metabolite extraction and urea-based protein extraction protocols followed by tryptic digest. Metabolites were analyzed after HILIC separation in positive and negative ionization mode and peptides were monitored by C18-RP LC-MS/MS. Fragment spectra were acquired by data-dependent and data-independent MS/MS measurements followed by data analysis with PEAKS Studio (Proteomics) and Mass Hunter Qualitative Analysis (Metabolomics). Preprocessing of metabolomics data was achieved with Mass Hunter Profinder and statistical analysis was performed with the R software.

Results

Reproducibility assessment (n=3, biological replicates) revealed that over 75% of metabolic features exhibited CVs <25% in both ionization modes. Proteome quantification likewise showed high quantitative reproducibility, evidenced by a median intra-run correlation coefficient of 0.96 across all measurements. Evaluation of fragment spectra enabled structural assignment and identification of >1000 protein groups. Only about ~11% of metabolic features (70 out of 651) could be assigned based on offline spectral library search (Metlin and Forensic/Toxicology database). Feasibility of the combined omics analysis to detect functionally relevant protein-metabolite interactions is demonstrated by coordinated changes observed between annotated metabolites (e.g. amino acids) and associated proteins (e.g. enzymes of threonine catabolism). Further application of the multi-omics approach to a larger cohort of liver tissue samples (n=34) allowed to detect significant (Benjamini-Hochberg adjusted p-values <0.05, spearman rho >0.7) associations between proteins and metabolites of unknown identity. Integrating fragment spectra information into molecular networks supplemented with proteomic data demonstrated to facilitate hypothesis-generating research and structural assignment of yet unidentified metabolic features.

Discussion

The presented approach utilizes tissue samples in an economic fashion by simultaneously increasing information yield through recovering metabolites and proteins from a single sample. As workflows for protein identification and subsequent pathway mapping are well established, non-targeted metabolomics experiments may benefit from additional proteomics information to facilitate integration of “unknowns” into functionally relevant metabolite-protein networks. This might help to overcome the limitation of low metabolite identification rates and hence support metabolic feature assignment and biomarker discovery in the future.

Rapid detection of TPMT and DPD mutations without DNA extraction using LAMP PCR

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 63

Ms. Charlotte Vandermeulen [1], ***Mr. Axel Giltay*** [1], ***Ms. Liselot Detemmerman*** [1]

1. *LaCAR MDx*

Thiopurine and fluoropyrimidine drugs are frequently used in various disease treatments, including cancer. Unfortunately, up to 30% of patients treated with these drugs can develop severe side effects, which can even lead to death. Metabolism of thiopurine drugs, such as azathiopurine, mercaptopurine and tioguanines are catalysed in competition by Thiopurine Methyltransferase (TPMT), Hypoxanthine Phosphoribosyltransferase (HPRT) and Xanthine Oxidase (XO). TPMT diverts a proportion of these drugs that are usually converted in the active drug, thioguanine nucleotides (6TGN), responsible for drug-related adverse effects. Consequently, TMPT activity is important for reducing the toxicity of thiopurine drugs. Fluoropyrimidines (i.g. 5-fluorouracil) cytotoxicity is related to the enzyme dihydropyrimidine dehydrogenase (DPD), which is crucial for the drug breakdown into nontoxic metabolites. Mutations on the DPYD gene are known to impede DPD activity and to lead to drug-related toxicity.

Adjusting dosage of these drugs in accordance to TMPT and DPYD enzyme activity is recommended by CPIC. To this aim, we developed two CE-marked kits, called LC-TPMT-LP and LC-DPD-LP, for the detection of *TPTM* and *DPD* mutations, directly from whole blood to minimize experimental time. LC-TPMT-LP detects 4 clinically relevant polymorphisms decreasing TPMT activity in patients; TPMT*2 (rs1800462), TPMT*3A (rs1142345 and rs1800460), TPMT*3B (rs1800460) and TPMT*3C (rs1142345). LC-DPD-LP detects 4 different SNPs, DPYD*2A (rs3918290), DPYD*13 (rs55886062), rs67376798 and rs56038477, all significantly affecting DPYD activity.

Whole blood is lysed in Lysis Buffer in a ratio 1/200 for 1-10 minutes. Afterwards, 5 µl of lysed sample is added to 20 µl Reaction Buffer for analysis. Each run contains a positive (heterozygous) and a negative control. Samples are determined by melting curve analysis following PCR amplification using LAMP technology. Change in fluorescence will be observed at a different temperature between homozygous mutated, heterozygous mutated or wild type, allowing to differentiate them. The different polymorphisms are detected using different reaction buffers in separate reactions.

Clinical validation consisted of the comparison of the LC-TPMT-LP and LC-DPD-LP detection results to the results of an accredited reference method. All mutations were identified with 100% accuracy. Both kits were tested for their repeatability and reproducibility by performing the same tests with two operators, two sample types, on two non-consecutive days and in duplicates. All results were as expected. Stability studies revealed that both kits can sustain 8 freeze thaw cycles and are stable at 4°C for 12 weeks. At -20°C both LC-TPMT-LP and LC-DPD-LP can be stored at least 2 years.

Our method allows for a rapid detection of the most relevant DPYP and TPMT mutations. Both kits can be used on the LC-Genie III, but also other rtPCR instruments. LC-TPMTP-LP kit can be used on the LightCycler 480 (I, II &Z) (Roche) or CFX96 (Bio-Rad) instruments. LC-DPD-LP kit can be used on the LightCycler 480 (I, II &Z) (Roche), LightCycler 96 (Roche), CFX96 (Bio-Rad) or Rotor-Gene Q (QIAGEN).

Identification of microRNA signatures is promising prognosis predictors for triple-negative breast cancer

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 72

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Introduction

Triple-negative breast cancer (TNBC) frequently recurrent within the first three to five years after treatment and shorter overall survival than other types of breast cancer. Therefore, evaluating the risk of recurrence in the early stage is critical for the treatment of TNBC. However, miRNA, the potential biomarker for prognosis of various cancers, seldom been considered as a set of signatures to predict relapse risk of TNBC. Here, we aimed to investigate whether a set of miRNA signatures could precisely predict the relapse risk for each patient after surgery.

Method

We applied the Gaussian mixture model (GMM) to identify a group of miRNA signatures from the differentially expressed miRNAs. Then, logistic regression used to build the prediction model with a group of miRNA signatures. To evaluate the performance, we incorporated a total of three cohorts from GEO and TCGA (TCGA_BRCA_TNBC, GSE40049, and GSE19783 datasets) as the training and validation sets. The schematic workflow for the identification of recurrence related miRNA signatures in Figure 1.

Result

The potential miRNA biomarkers of TNBC were identified with the differentially expressed method. Using logistic regression and Gaussian mixture model (GMM), we successfully identified a set of miRNA signatures for the relapse risk prediction from the potential TNBC miRNA biomarkers (Figure 2) and developed the prediction model (Figure 3). Evaluating the performance of the logistic regression model, the set of signatures can provide high accuracy prediction for relapse of TNBC patients with the AUC of 79% from the TCGA training dataset (Figure 4). Furthermore, the accuracy of validation was 73.95% from GSE40049 (N=24) and 100% from GSE19783 (N=18) datasets.

Discussion

In conclusion, the group of miRNA signatures prediction model developed in this study may help clinicians to provide an option of adjuvant treatment for high-risk recurrence after surgery patients in TNBC.

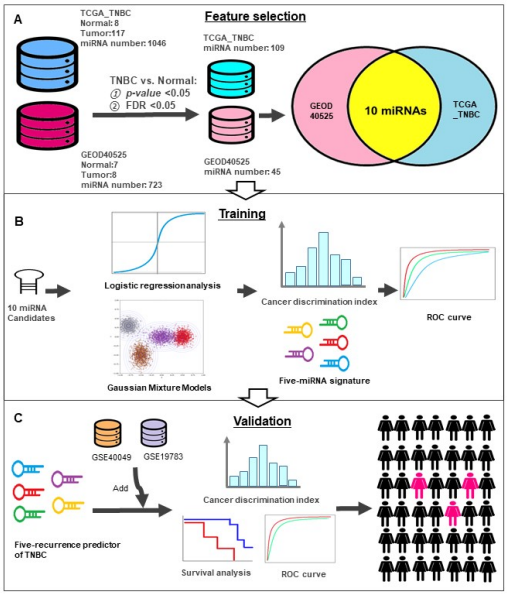

Fig 1. Schematic workflow for the identification of recurrence-related miRNA predictor in TNBC.

Fig 1 schematic of the bioinformatics workflow.jpg

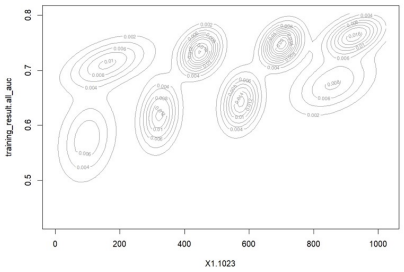

Fig 2. The pattern of AUC and 1023 logistic regression models were based on Gaussian finite mixture models.

Fig 2. the pattern of auc and 1023 logistic regression models were based on gaussian finite mixture models.jpg

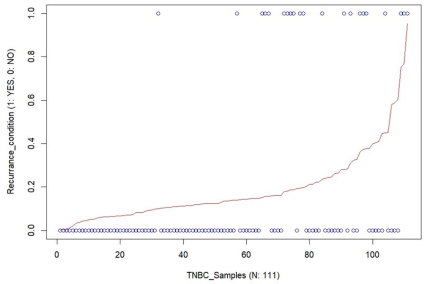

Fig 3. MiRNA expression across all data is assigned to patient condition. The x-axis is a combination of TNBC patients.

Fig 3. mirna expression across all data is assigned to patient condition. the x-axis is a combination of tnbc patients.jpg

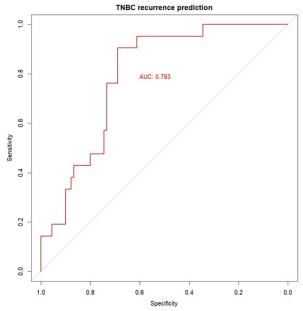

Fig 4. Predictive value of the five-miRNA signature in 111 TNBC patients. The ROC for TNBC recurrence by five-miRNA signature between patients with or without recurrence in the combined.

Fig 4. predictive value of the five-mirna signature in 111 tnbc patients.jpg

Outcome Definition Influences the Relationship Between Genetic Polymorphisms of ERCC1, ERCC2, SLC22A2 and Cisplatin Nephrotoxicity in Adult Testicular Cancer Patients

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 58

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Although previous research identified candidate genetic polymorphisms associated with cisplatin nephrotoxicity, varying outcome definitions potentially contributed to the variability in the effect size and direction of this relationship. We selected genetic variants that have been significantly associated with cisplatin-induced nephrotoxicity in more than one published study (*SLC22A2* rs316019; *ERCC1* rs11615 and rs3212986; *ERCC2* rs1799793 and rs13181) and performed a replication analysis to confirm associations between these genetic polymorphisms and cisplatin nephrotoxicity using various outcome definitions. We included 282 germ cell testicular cancer patients treated with cisplatin from 2009–2014, aged >17 years recruited by the Canadian Pharmacogenomics Network for Drug Safety. Nephrotoxicity was defined using four grading tools: (1) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 for acute kidney injury (AKI) or CTCAE-AKI; (2) adjusted cisplatin-induced AKI; (3) elevation of serum creatinine; and (4) reduction in the estimated glomerular filtration rate (eGFR). Significant associations were only found when using the CTCAE v4.03 definition: genotype CA of the *ERCC1* rs3212986 was associated with decreased risk of cisplatin nephrotoxicity (OR_{adj} = 0.24; 95% CI: 0.08–0.70; p = 0.009) compared to genotype CC. In contrast, addition of allele A at *SLC22A2* rs316019 was associated with increased risk (OR_{adj} = 4.41; 95% CI: 1.96–9.88; p < 0.001) while genotype AC was associated with a higher risk of cisplatin nephrotoxicity (OR_{adj} = 5.06; 95% CI: 1.69–15.16; p = 0.004) compared to genotype CC. Our study showed that different case definitions led to variability in the genetic risk ascertainment of cisplatin nephrotoxicity. Therefore, consensus on a set of clinically relevant outcome definitions that all such studies should follow is needed.

MicroRNAs downregulate drug metabolizing enzymes and transporters in inflammation

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 60

Mrs. Nicole Kugler [1], ***Dr. Kathrin Klein*** [1], ***Prof. Ulrich M. Zanger*** [1]

1. *Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology Stuttgart and Eberhard Karls University, Tuebingen*

Introduction: Hepatic detoxification capacity is impaired in conditions of acute and chronic inflammation due to coordinated downregulation of drug metabolizing enzymes and transporters (DMET). Underlying mechanisms have not been completely clarified so far. We conducted a study of genome-wide gene expression of liver tissues to investigate the impact of inflammation. Since microRNAs (miRNAs) act as post-transcriptional regulators, we investigated their role in inflammation-related downregulation of DMET.

Methods: Microarray analyses were performed to investigate genome-wide gene and miRNA expression patterns in livers from patients with elevated inflammation marker C-reactive protein (CRP). Correlation analysis between miRNA expression and cytochrome P450 (CYP) phenotypes was conducted. Predicted 3'UTR binding sites of upregulated miRNAs in ADME genes were validated using luciferase reporter constructs. HepaRG cells were transfected with miRNA mimics. ADME gene expression was relatively quantified by qPCR and six CYP enzyme activities were measured using a cocktail LC-MS/MS assay.

Results: Livers of patients with elevated CRP showed patterns of positive and negative acute phase response including downregulation of DMET. We identified 40 differentially expressed miRNAs, for instance miR-155-5p, associated with elevated CRP. Expression of inflammation-associated miRNAs showed negative correlations to ADME genes (up to r_s = -0.6). MicroRNA binding sites in RXRα (miR-130b-3p), CYP2C8 (miR-452-5p), CYP2C9 (miR-155-5p), CYP2C19 (miR-155-5p, miR-6807-5p), and CYP3A4 (miR-224-5p) were validated. Transfected HepaRG cells showed reductions in mRNA levels of ADME (40-80%) and CYP enzyme activities, especially for miR-155 (20-50%).

Discussion: Inflammation-associated miRNAs were identified showing negative correlations to ADME expression. This suggests a negative regulation of ADME genes by these miRNAs. Furthermore, some of these miRNAs were able to downregulate ADME genes, indicating a contribution to the coordinated downregulation of DMET in inflammatory conditions.

This study was supported by the Robert Bosch Foundation, Stuttgart, Germany.

ABT-199 and Bortezomib Synergistically Induce Apoptosis in Soft-Tissue Sarcomas

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 59

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Introduction: Soft-tissue sarcomas (STS) are mesenchymal malignancies with high heterogeneity that predominantly affect children and young adults. Despite routinely applied therapy strategies including radiotherapy, surgery and chemotherapy, the five-year survival rates of metastatic STS diseases is only 50 %. Therefore, it is of high importance to focus on possible combinational therapies for the effective treatment of all kinds of STS regardless of their heterogeneous nature.

For such a therapy we combined the clinically approved BH3-mimetic drug ABT-199 (Venetoclax) with the proteasome inhibitor Bortezomib (Velcade). ABT-199 selectively inhibits the anti-apoptotic protein Bcl-2 whereas the proteasome inhibitor Bortezomib is effective, e.g., in multiple myeloma.

Methods: Sarcoma cell lines were incubated with ABT-199 and Bortezomib alone or in combination and subsequently apoptotic cell death was detected by flow cytometric analysis of relative mitochondrial membrane potential (TMRM) and exposure of phosphatidyl serine (Annexin V). In order to elucidate a possible mechanism for the observed cell death, we analyzed expression of several members of the Bcl-2 family involved in the apoptosis pathway by Western Blotting.

Results: Intriguingly, combined treatment with ABT-199 and Bortezomib showed synergistic cell death induction in a number of sarcoma cell lines including Rhabdomyosarcoma, Leiomyosarcoma and Synovial sarcoma. Loss of mitochondrial membrane potential and phosphatidyl serine exposure revealed apoptosis as the underlying cell death mechanism induced by the combinational treatment. Interestingly, the expression of Bok, a homologue of the pore-forming effector proteins Bax and Bak, was increased in response to drug treatment. In addition, expression was simultaneously increased for both, the BH3-only protein Noxa and its interaction partner Mcl-1, a pro-survival Bcl-2 protein. Strikingly, the sarcoma cell line SW982 revealed reduced apoptosis sensitivity in response to ABT-199/Bortezomib in single knock-out (KO) of all effector proteins Bax, Bak and Bok with the most significant reduction in Bax KO. An additional knock-down of Noxa in these KO cell lines significantly reduced cell death compared to Noxa knock-down alone.

Discussion: ABT-199 and Bortezomib synergistically induced apoptotic cell death in various sarcoma cell lines concomitant with enhanced expression of the Bcl-2 proteins Bok, Noxa and Mcl-1. Hence, we suggest a mechanism in which the concomitant inhibition of anti-apoptotic Blcl-2 proteins by ABT-199 and the stabilized pro-apoptotic proteins shift the equilibrium towards apoptosis. Reduced apoptosis induction in Bax, Bak, Bok and Noxa deficient cells indicate that these Bcl-2 proteins are indispensable for the observed synergistic effect. Taken together, our results revealed the combined treatment with ABT-199 and Bortezomib as a new and highly promising therapy option for advanced STS. Future efforts, e.g. simultaneous knock-out of relevant Bcl-2 proteins, will unravel the underlying mechanism of the observed synergistic cell death induction by ABT-199 and Bortezomib.

Effects of a common 8 bp duplication at the exon7-intron7 border on OCT1 splicing, expression, and function

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 65

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Organic cation transporter 1 (OCT1) is localized in the sinusoidal membrane of human hepatocytes, where it mediates the uptake of clinically relevant drugs and endogenous compounds. OCT1-mediated uptake may represent a limiting step in the hepatic clearance of these compounds. OCT1 is genetically highly variable. Common amino acid substitutions and deletions are known to confer altered pharmacokinetics and efficacy of drugs like sumatriptan, fenoterol, and morphine in 9% of Europeans and White Americans. Recently, the splice variant rs35854239 was suggested to also affect OCT1 function. rs35854239 is an 8 bp duplication at the exon 7-intron 7 border which leads to a duplication of the donor splice site and therefore may affect splicing of OCT1.

In this study, we quantified the effect of rs35854239 on OCT1 splicing using pyrosequencing and next-generation sequencing in HepG2 und Huh7 cells and in human liver samples. We also analyzed the effects of rs35854239 on OCT1 mRNA expression, the localization and activity of the resulting OCT1 protein, and on the pharmacokinetics of sumatriptan and fenoterol.

To quantify the effects on splicing, we transfected HepG2 and Huh7 cells with a mini-gene construct containing exon 7 of OCT1 with and without the 8 bp duplication (rs35854239) and compared the amounts of correctly and alternatively spliced transcripts 48 h and 72 h after transfection. The 8 bp duplication caused alternative splicing in 38% (next-generation sequencing) and 52% (pyrosequencing) of the mini-gene transcripts. The alternatively spliced transcript encodes for an OCT1 protein that is truncated after transmembrane domain 9. This truncated protein was not localized at the plasma membrane and was not able to transport the OCT1 model substrate ASP^+ after overexpression in HEK293 cells. In human liver samples, however, the alternatively spliced OCT1 transcript was detectable only at very low levels (0.3% in heterozygous and 0.6% in homozygous carriers of the 8 bp duplication). This may be due to non-sense mediated mRNA decay of the alternatively spliced transcripts. In addition, the 8 bp duplication was not associated with reduced OCT1 mRNA expression in human liver samples and more importantly was not associated with significant changes in the pharmacokinetics of sumatriptan and fenoterol.

In conclusion, the rs35854239 variant at the exon 7-intron 7 border of OCT1 leads to alternatively spliced transcripts that code for an inactive OCT1 protein. Although clearly detectable in mini-gene setting, the alternatively spliced transcript is barely detectable in human liver samples and has no substantial effect on total OCT1 mRNA expression. Therefore, although very common, the rs35854239 variant may have only limited therapeutic relevance.

CYP4F2 rs2108622 Genotyping for Warfarin Dosing in Indian Patients

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 68

Dr. Swarup Shah [1], ***Dr. Minal Paradkar*** [1], ***Dr. Sripriya Natarajan*** [1], ***Dr. Chandrashekhar Ponde*** [1], ***Dr. Rajesh Rajani*** [1], ***Dr. Tester Ashavaid*** [1]

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Introduction

The large inter-individual variability and narrow therapeutic index of warfarin has made dose management challenging. Recent literature recommends genetic testing for *CYP4F2* genetic variant along with *VKORC1* and *CYP2C9* variants for effective warfarin dose management. Therefore the present study aimed to determine the *CYP4F2* rs2108622 allele frequency as well as its impact on warfarin dose management in Indian patients.

Method

The present ongoing study has led to recruitment of 95 patients on warfarin therapy. Patients mean daily warfarin dose, international normalized ratio (INR) and demographics were recorded. A multiplex allele-specific PCR assay was developed using the positive DNA controls for *VKORC1* [c.1173C>T], *CYP2C9* [*2, *3], *CYP4F2* [C.1297G>A] variants and the results were validated by Sanger sequencing. Genotype frequencies were tested for Hardy-Weinberg equilibrium. Krushal-Wallis and Chi-square test were performed for comparison of warfarin dose and INR with *CYP4F2* mutants using Graphpad Prism (v7.02).

Result

The mutant allele frequencies for *VKORC1* [c.1173C>T], *CYP2C9* [*2, *3], *CYP4F2* [C.1297G>A] variants were found to be 0.14, 0.05, 0.13 and 0.41 respectively. The mean warfarin doses as well as the mean INR were not statistically significant with *CYP4F2*genotypes. Importantly, only 47% of patients with supra [>3.0] and sub-therapeutic [<2.0] INR were explained by *VKORC1*and *CYP2C9* genotyping, which was significantly increased to 79% with inclusion of *CYP4F2*genotyping. Further in the above subgroup, 63% of patients with *CYP2C9*+*VKORC1*wild-type showed the presence of *CYP4F2*variant. Similar association between *CYP4F2*variant and supra and sub-therapeutic warfarin dose was also observed.

Discussion

The present study, a first from Western India showed that the inclusion of *CYP4F2*genotyping has significant impact on warfarin dosing thereby strongly suggesting preemptive *CYP4F2* genotyping for patient on warfarin therapy. Also the multiplex PCR assay developed is sensitive, rapid and cost-effective genetic screening tool for warfarin dosing.

Precision medicine for molecular profiling of metastatic or advanced cancers: An experience of a tertiary Chilean health center

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 77

Dr. Marcelo Garrido [1], Mr. Miguel Cordova [2], Mr. Matias Muñoz [1], Dr. Ignacio Retamal [1], Dr. María Loreto Bravo [1], Dr. Mauricio Pinto [2], Dr. Benjamin García-Bloj [3]

1. *Department of Hematology and Oncology, School of Medicine, Pontificia Universidad Católica de Chile,* ***2.*** *Deparment of Hematology and Oncology, School of Medicine, Pontificia Universidad Católica de Chile,* ***3.*** *Escuela de Medicina, Facultad de Ciencias, Universidad Mayor and Magenta Genetics*

BackgroundIndividualized targeted therapy for metastatic/advanced cancer using high-throughput genomic profiling is becoming increasingly common in the clinical practice. However, the interpretation of these data in order to provide the best pharmacological options can be a challenge for oncologists. Here, we present the experience of a unique tertiary health center in precision medicine.

MethodsComprehensive molecular profiles were obtained from 38 advanced cancer patients by NGS platforms. Results and pharmacological options were discussed in internal tumor boards.

Results Mutational profiles were obtained for all patients. In 37 (97.4%) we found a clinically relevant mutation. The most frequent cancer types were colorectal (26.6%), pancreatic (10.5%), gastric cancer (7.9%) and gastrointestinal stromal tumor (7.9%). The most common mutations were found in *TP53* (45%), *APC* (24%), *KRAS* (21%) , *ARID1A* (13%) and *KIT/BRAF/BRCA2/HGF* (8%). Interestingly, the pathogenic *MUTYH* (c.1187G> A, p.Gly396Asp) germline mutation in was found in 3 out of 38 patients (7.9%). On the other hand, actionable mutations with *on label*and *off label*therapy recommendations were found in 44.7% and 26.3 % of patients, respectively. Finally, in 22 (57%) cases, an individualized treatment or change in therapeutic behavior was determined after the molecular profiling.

ConclusionsOur findings suggest that a high proportion of advanced cancer patients could benefit from targeted therapies guided by tumor sequencing. However, according to our experience, applying molecular profiling into the clinical practice is still a pending challenge.

The role of genetic variants in ADME genes in methotrexate-induced toxicities in patients with osteosarcoma

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 74

Ms. Marije Klumpers [1], ***Ms. Evelien Hurkmans*** [1], ***Dr. Sita Vermeulen*** [1], ***Dr. Melanie Hagleitner*** [2], ***Dr. Uta Flucke*** [1], ***Prof. Bart Schreuder*** [1], ***Prof. Hans Gelderblom*** [3], ***Dr. Johannes Bras*** [4], ***Prof. Henk Jan Guchelaar*** [3], ***Dr. Marieke Coenen*** [1], ***Dr. Maroeska te Loo*** [1]

1. *Radboud university medical center, Nijmegen,* ***2.*** *Princess Máxima Center for Pediatric Oncology, Utrecht,* ***3.*** *Leiden University Medical Center, Leiden,* ***4.*** *Academic Medical Center, Amsterdam*

Introduction

High-dose methotrexate (HD-MTX) is a cornerstone agent in the chemotherapeutic treatment of patients with osteosarcoma. Due to interindividual variation in MTX metabolism, patients often develop HD-MTX-induced toxicities, which cannot always be prevented by MTX plasma level monitoring. We aim to identify determinants of HD-MTX-induced toxicities in osteosarcoma patients, by investigating the relation between MTX plasma levels and toxicities, and the contribution of genetic variants in genes related to drug absorption, distribution, metabolism and elimination (ADME).

Methods

A cohort of 114 osteosarcoma patients was genotyped for 1,931 variants in 231 genes using the Drug Metabolism Enzymes and Transporters Plus array. Laboratory results during and after HD-MTX treatment concerning renal function (creatinine), liver damage (aspartate aminotransferase, alanine transaminase) and myelopoiesis (thrombocytes, leukocytes, neutrophils, hemoglobin) were obtained to reflect toxicity outcomes. Relevant clinical variables were tested for association for each outcome, and included in the model if needed. Associations were tested between 48-hour MTX plasma levels and toxicity data, and genetic association analyses between outcomes and ADME genetic variants were performed using generalized estimating equations to take repeated measurements into account.

Results

Analyses of data concerning 1,238 HD-MTX courses identified no association between 48 hour MTX plasma levels and toxicities outcomes in our cohort. Genetic association analyses resulted in three genetic variants statistically significantly associated with pharmacokinetic or toxicity outcomes (after Bonferroni correction). One of the these variants was significantly associated with lower 48 hour MTX plasma levels, being the 5'UTR variant rs3736599 in *SULT1E1*(coef -0.313 [95% CI -0.459 – -0.167]; p=2.60×10^{-5}). Analysis with toxicity markers resulted in significant associations between three variants in two genes (representing two independent loci due to high linkage disequilibrium) and HD-MTX induced decreased thrombocyte counts. These included two intronic variants in *CYP2B6*: rs4803418 (coef -0.187 [95% CI -0.275 – -0.099]; p=3.04×10^{-5}) and rs4803419 (coef -0.186 [95% CI -0.278 – -0.093]; p=8.80×10^{-5}), and the intronic variant rs4808326 in *CYP4F8*(coef 0.193 [95% CI 0.099 – 0.287]; p=6.02×10^{-5}).

Discussion

To date, all the statistically significantly associated variants identified in our study were not known to play a role in MTX pharmacokinetics or -dynamics, nor were they previously found to have an influence on the development and severity of thrombocytopenia, or other comparable phenotypes. Validation of these variants in an independent cohort and further functional investigation of variants in the identified genes is needed to study if and how they affect MTX plasma levels and the development of HD-MTX-induced toxicities.

Multi-label classification of geriatric depression and anxiety using a low-cost activity tracker

Thursday, 20th February - 13:30: Poster Presentation (Main Hall) - Poster - Abstract ID: 80

Prof. Mun-Taek Choi [1], ***Mr. Jae-Kyeong Sim*** [1]

1. *Sungkyunkwan University*

Understanding geriatric mood disorders, especially depression and anxiety, is important because those are common symptoms of dementia. Usually, depression and anxiety are clinically screened by the Geriatric Depression Scale (GDS) and the Geriatric Anxiety Inventory (GAI), respectively. Since GDS and GAI are self-report-based assessments, it is known to be inconvenient to patients or families and even inaccurate sometimes.

Depression and anxiety are known to be associated with the disruption of a 24-hour activity rhythm and sleep. In order to find the 24-hour activity rhythms and sleep patterns of patients, 265 subjects with clinically-diagnosed mild cognitive impairment (MCI) between 60 and 90 years old in Korea participated in this study. The activity data of the subjects were collected over several weeks per subject wearing a wrist watch-type low-cost activity tracker. Based on a circadian rhythm, we extracted features for 24-hour activity rhythms and sleep patterns from the time-series activity data.

Diagnosing depression and anxiety is a problem of multi-label nature since a subject can be diagnosed with depression, anxiety or both. In order to understand the association between the diagnosis of depression and anxiety and 24-hour activity rhythms and sleep patterns, we applied multi-label classification in machine learning using binary relevance (BR) that creates an independent binary classification for each label. We tried various classification algorithms for each label and compared the performances to find the best classifier among the algorithms per label.

The results show that the best classifier is the combination of random forests for depression and gradient boosting for anxiety, with an average F1 score of 77.4%. In addition, confusion matrices for both classifiers showed fairly high prediction by the classifiers for non-mood and mood disorders. Although the results are not sufficient for clinical use immediately, the use of low-cost activity trackers has shown the potential for classification of geriatric mood disorders.

Our study has yielded the following meaningful results in developing a classifier that understands the relationship between the diagnosis of geriatric depression and anxiety and the activity and sleep patterns of the elderly. First, six features of the 24-hour activity rhythm showed the possibility of simplifying the diagnosis of depression and anxiety. Second, it showed the possibility of using low-cost activity trackers as an alternative to paper-based or complex assessments. Third, this study presented the basic frame of a diagnostic assistant system that doctors can easily use in the field.

This study has the following limitations. The number of data used in this study is relatively small. We need more data to increase the generality of the classification performance. In addition, although the best F1 score in this study is not low, we need to add more data or find other features to improve classification performance for clinical use.

Performance scores for multi-label classification on the test set

Depression Classifier	Anxiety Classifier	Precision	Recall	F_1
RFC	GBC	0.8	0.75	0.774

Confusion matrix of RFC for depression classification

		Predicted:	
		Non-depression	Depression
Actual:	Non-depression	7	1
	Depression	2	6

Confusion matrix of GBC for anxiety classification

		Predicted:	
		Non-anxiety	Anxiety
Actual:	Non-anxiety	6	2
	Anxiety	2	6

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Identifying gut microbiome contributions to drug metabolism

Thursday, 20th February - 14:30: Plenary Speeches: Precision Medicine and OMICS (Auditorium) - Plenary Speech - Abstract ID: 17

Dr. Michael Zimmermann [1]

1. *European Molecular Biology Laboratory, Heidelberg*

Individuals vary widely in their drug responses, which can be dangerous and expensive due to significant treatment delays and adverse effects. Growing evidence implicates the gut microbiome in this variability, however the molecular mechanisms remain mostly unknown. Using antiviral nucleoside analogues and clonazepam as examples, we recently reported experimental and computational approaches to separate host and gut microbiota contributions to drug metabolism. The resulting pharmacokinetic models identified measurable physiological, microbial and chemical parameters that dictate host and microbiome contributions to the metabolism of xenobiotics. To systematically map the drug metabolizing capacity of the gut microbiota and assess its potential contribution to drug metabolism, we further measured the ability of 76 diverse human gut bacteria to metabolize each of 271 oral drugs. We found that two thirds of these drugs are chemically modified by at least one of the tested microbes. Through combination of high-throughput bacterial genetics with mass spectrometry, we systematically identified drug-metabolizing microbial gene products. These gene products better explain the drug-metabolizing capacity of bacterial strains than their phylogenetic classification. We further demonstrate that the abundance of homologs of these gene products predict the capacity of complete human gut communities to metabolize the targeted drugs. These causal links between microbiota gene content and metabolic activities connect inter-individual microbiome variability to interpersonal differences in drug metabolism, which has translatable potential on medical therapy and drug development across multiple disease indications.

Gut Microbiota Dysbiosis in Human Obesity: Impact of Bariatric Surgery

Thursday, 20th February - 15:00: Plenary Speeches: Precision Medicine and OMICS (Auditorium) - Plenary Speech - Abstract ID: 121

Prof. Karine CLEMENT [1]

1. *Sorbonne Université/INSERM*

The gut microbiota is a recently described organ involved in many physiological functions all of which playing important roles in host health. Mouse studies including transfer of microbiota from mice or humans into germ-free mice have demonstrated that the gut microbiota could be a relevant player in obesity pathophysiology. Human studies also reported obesity is associated with major perturbations of the gut microbiota diversity, composition and function (i.e. dysbiosis) albeit with major inter individual variability. This dysbiosis is exacerbated in patients with severe obesity who are candidate to bariatric surgery. The number of bariatric surgeries reserved for the most severe cases associated with comorbidities increases in parallel with obesity epidemics. Studies in mice and human has shown that bariatric surgery procedures dramatically modify gut microbiota composition and function but after gastric bypass the rescue of gut microbiota is incomplete. Some changes in gut microbiota composition are however associated with improvement in clinical outcomes including improved corpulence and reduced inflammation. These changes are not always consistent and vary across populations. Further research efforts are thus needed to deepen the understanding of individual gut changes on in obesity and improved metabolism after bariatric surgery. A challenge is to provide evidence for the need to act therapeutically on the gut microbiota to improve each patient outcome in the long term. This has to be considered in a precision medicine approach. This lecture will address these aspects looking at the future of personalized medicine in this field.

Single-cell analyses reveals principles of gene expression in space, time, and during disease.

Thursday, 20th February - 15:30: Plenary Speeches: Precision Medicine and OMICS (Auditorium) - Plenary Speech - Abstract ID: 137

Prof. Nikolaus Rajewsky [1]

1. *Max Delbrück Center for Molecular Medicine*

I will explain recent advances, including our own contributions, in single-cell (multi)omics. I will present unpublished data and show how we can discover design principles of how gene expression drives life in (tissue)-space & time. I will argue that these approaches will transform not only basic science but also clinical pathology, diagnosis, and therapy. I will discuss the specific challenges for Machine Learning in this transformation.
I will then present LifeTime, a pan-European Consortium of 90 research institutions and 80 companies that aims to improve healthcare by mapping, understand and target human cells in disease progression by integrating Machine Learning with single-cell multiomics and organoids.

Digital Health: Challenges for Research and Future Medicine

Thursday, 20th February - 16:30: Plenary Speeches: Artificial Intelligence and Digital Medicine (Auditorium) - Plenary Speech - Abstract ID: 87

Dr. Naveed Ishaque [1], ***Dr. Christian Conrad*** [1], ***Mr. Juergen Eils*** [1], ***Mr. Jeongbin Park*** [1], ***Dr. Julia Jabs*** [2], ***Dr. Mohammed Abba*** [3], ***Prof. Heike Algayer*** [3], ***Prof. Roland Eils*** [1]

1. *Berlin Institute of Health and Charité Universitätsmedizin Berlin,* ***2.*** *Merck,* ***3.*** *UNIVERSITÄTSMEDIZIN Mannheim*

Recent technological breakthroughs in high throughput biological profiling methods have been the driving force behind advances in precision and personalized medicine. In particular, we have seen the success adoption of genome, transcriptome and epigenome profiling for diagnosis, predictive outcomes, and therapy recommendations for disease. However, multi-faceted heterogeneity represents a major challenge – disease, patient and sample heterogeneity introduce additional complexity in unraveling the molecular determinants of health and disease.

To successfully implement efficient pipelines and workflows for precision medicine, there is also a need for advancing data automation and integration, computational infrastructure, personalized model systems, and applications of artificial intelligence and machine learning.

In this talk I will present some of our recent efforts to unravel heterogeneity in human disease and a general overview how the newly established Digital Health Centre at the Berlin Institute of Health and Charite University Hospital is contributing to the effort of advancing the field of precision medicine. Specific topics covered will include low cost tumor diagnostics using DNA sequence and methylation data, implications of tumor evolution on precision medicine, analysis of *in-situ* transcriptomics data, and drug screening in *ex-vivo*models.

Deep learning to assist the identification of neoantigens

Thursday, 20th February - 17:00: Plenary Speeches: Artificial Intelligence and Digital Medicine (Auditorium) - Plenary Speech - Abstract ID: 19

Dr. Mathias Wilhelm [1], ***Dr. Daniel Zolg*** [1], ***Mr. Michael Graber*** [1], ***Mr. Siegfried Gessulat*** [1], ***Mr. Tobias Schmidt*** [1], ***Prof. Bernhard Kuster*** [1]

1. *Chair of Proteomics and Bioanalytics, Technical University of Munich*

The mass spectrometric identification of tumor specific HLA class I peptides as candidates for immunotherapy is making rapid progress over the last years. However, the yield of such peptides is impaired by the quality of the immunoaffinity purification and technical limitations of the chromatography and mass spectrometric analysis. Especially the latter poses specific statistical challenges because current methods for peptide identification fail to confidently differentiate correct from incorrect matches due to the nature of the short non-tryptic HLA peptides. Within the ProteomeTools project (www.ProteomeTools.org), ~240.000 such HLA class I and II peptides were synthesized and systematically characterized. In conjunction with >500.000 synthetic tryptic peptides these synthetic standards were used to train our deep neural network Prosit, which is now able to prediction the expected tandem mass spectrum of any peptide sequence with very high accuracy (R>0.97). These predictions can now be used to aid the process of HLA peptide identification by comparing the measured and expected tandem mass spectra. This allows the very efficient separation of correct and incorrect matches and thus increases the number of confidently (1% FDR) identified HLA class I peptides by ~2 fold, in turn significantly boosting the chances of finding disease/patient-specific HLA markers and candidates for immunotherapy.

How to Consider Rare Genetic Variants in ADME genes for Personalized Drug Therapy.

Friday, 21st February - 09:15: Plenary Speeches: ADME and Personalized Therapy (Auditorium) - Plenary Speech - Abstract ID: 92

Prof. Volker Lauschke [1]

1. *Karolinska Institutet*

Variability in genes implicated in drug pharmacokinetics or drug response can modulate treatment efficacy or predispose to adverse drug reactions. With the advent of population-scale sequencing, it became evident that pharmacogenomic variability is complex, comprising a plethora of rare single nucleotide variants (SNVs), indels and copy number variations (CNVs). Most of these rare variants are not evaluated using conventional SNP arrays and have not been experimentally characterized. Thus, if and how information about such variants can be incorporated into drug response predictions constitutes an ongoing area of debate.

Key questions arising in this context are: How much impact do rare variations have on drug response and toxicity? How can we interpret such variants for which no experimental characterizations are available? What is needed to be able to incorporate rare variant information into clinical pharmacogenetic decision-making?

In this talk I aim to address these questions by first providing an overview of the genomic complexity of pharmacogenes, followed by a critical evaluation of the methodological tool kit that is available today for the interpretation of rare pharmacogenetic variants. Based on these methods, I will give recent quantitative estimates for the relative importance of rare genetic variability on drug response phenotypes and indicate a roadmap of how such results could be utilized in a clinical setting. The main part of the talk will be focused on the evaluation of genetic complexity in ADME genes; however, I will also present ongoing computational and experimental work about the systematic evaluation of drug target variations.

Genotype-guided fluoropyrimidine dosing: ready for implementation

Friday, 21st February - 09:45: Plenary Speeches: ADME and Personalized Therapy (Auditorium) - Plenary Speech - Abstract ID: 118

Dr. Ursula Amstutz [1]

1. *Inselspital Bern University Hospital and University of Bern*

The impact of genetic variation in the dihydropyrimidine dehydrogenase gene (DPYD) on the individual risk of severe toxicity from chemotherapy with fluoropyrimidines was first described over twenty years ago. However, the clinical benefits of genotype-guided fluoropyrimidine dosing have only recently been demonstrated in prospective studies. Here, an overview over the discovery and replication of associations between four key DPYD risk variants and fluoropyrimidine-related toxicity will be presented together with the most recent evidence-based clinical practice recommendations for genotype-guided dosing, evidence from studies evaluating the implementation of prospective DPYD testing, and a discussion of combining DPYD testing with therapeutic drug monitoring for further therapy optimization and individualization. Used initially as a textbook example of a pharmacogenetic syndrome during the early days of pharmacogenetic research, DPYD testing in patients receiving fluoropyrimidine-based chemotherapy now indeed serves as one of only few examples for a pharmacogenetic test related to drug metabolism that is gaining uptake in clinical practice.

EATRIS-Plus: the development of a multiomic toolbox for performing high-quality research in Personalised Medicine

Friday, 21st February - 10:45: Oral Session: Emerging opportunities in personalized medicine, cutting-edge new strategies and solutions (Auditorium) - Oral - Abstract ID: 73

Ms. Anne-Charlotte Fauvel [1], Dr. Florence Bietrix [1], Dr. Andreas Scherer [2], Prof. Alain Van Gool [3], Prof. Peter-Bram 't Hoen [3], Prof. Marian Hajduch [4], Dr. antonio andreu [1]

1. *EATRIS,* ***2.*** *FIMM,* ***3.*** *Radboudumc,* ***4.*** *IMTM*

Efficient advancement of Personalised Medicine depends on the availability of validated patient-targeted biomarkers. However, as our capacity to identify genetic variants associated with complex diseases increases, these do not fully recapitulate the resulting disease phenotypes, and a more precise understanding of the molecular profiles are needed. This realisation provides a rationale for the development of multi-omic approaches. In order to turn the multi-omic promises into a reality, systemic bottlenecks impacting the biomarker field needs to be overcome:

- Poor levels of technological and analytical harmonisation;
- Poor data stewardship and compliance to the FAIR (Findable, Accessible, Interoperable, and Reusable) principles;
- Lack of understanding of the relationship between genomic biomarkers and downstream molecular markers (transcriptomic, proteomic, metabolomic, among others);
- Lack of reliable control reference values for these biomarkers in healthy populations; and
- Poor understanding of the clinical needs resulting in limited clinical adoption.

Tackling those issues in a systematic way is one of the objectives of**EATRIS-Plus**, a H2020-funded project to kick start early 2020. With 19 partners across 13 countries, the consortium ambitions to deliver a multi-omic toolbox to support cross omic analysis and data integration in clinical samples.
This toolbox will contain:

- Consensus-based SOPs for omic technologies;
- Guidelines for omic analytical processes;
- Validated reference materials for analytical processes;
- Quality parameters for benchmarking quality assessment activities;
- Data analytical and FAIRification tools;
- Criteria for establishing reference values in population cohorts;
- Troubleshooting guidelines;
- Access to a repository of multi-omic reference values

The omic tools will be developed and tested with a real-setting demonstrator, an already established cohort of 1,000 healthy individuals in Czechia upon whom genomic sequencing has been already performed. Information available on this healthy individual cohort will be augmented during the project with transcriptomic, proteomic and metabolomic data.
By providing such toolbox to the research community, EATRIS-Plus will be the engine to enable high-quality research in the context of patient stratification and accelerate the implementation of Personalised Medicine solutions.
EATRIS is the European Infrastructure for Translational Medicine providing services for accelerating biomedical innovation.

Can Cipherome's algorithm predict warfarin adverse drug reaction using a drug safety score incorporating both common and rare pharmacogenomic variants?

Friday, 21st February - 11:05: Oral Session: Emerging opportunities in personalized medicine, cutting-edge new strategies and solutions (Auditorium) - Oral - Abstract ID: 79

Mr. Brian Ryu [1], ***Dr. In Gu "Sean" Lee*** [1], ***Dr. Jane Chiang*** [1]

1. *Cipherome, Inc.*

Introduction:

A computational approach to decipher variant-gene-drug combinations and enables physicians to prescribe the best drug with the least potential for harm out is needed. This study determines if Cipherome's algorithm (CA), an aggregate, drug safety score (DSS) generated from an individual's genomic profile (using common and rare genetic variants), can predict the likelihood of warfarin adverse drug reactions (ADRs), such as major bleeding or hemorrhagic events.

Methods:

We conducted a retrospective analysis using genomic and phenotypic data from the UK Biobank **(Table 1).** Study inclusion criteria included individuals on the first 90 days of warfarin administration with ADR records (per ICD 9/10 codes and whole exome sequencing (WES) data (n = 630). Most common ADRs listed in the health registry data comprised non-traumatic hemorrhage, gastrointestinal bleeding, and "ADRs due to anticoagulant use". CA generated a DSS for each individual (0-1, closer to 0 indicating a higher likelihood of warfarin ADR). A cut-point at 0.2 was established based on prior research for DSS distribution, with the score demonstrating a clear bimodal occurrence and demarcation at 0.2 **(Figure 1).** We divided the groups into ADR (+) / ADR (-) and DSS less than 0.2 (higher ADR risk) and greater than or equal to 0.2 (lower risk) and used the Fisher's exact test to generate an Odds Ratio (OR) to determine ADR likelihood given the DSS. We used R and python to process all health registry data, and R packages for all statistical tests.

Results:

Based on ICD 9/10 codes, individuals were identified as ADR (+) (n=28) and ADR (-) (n=602), with DSS < 0.2 (n=65) and > 0.2 (n=565) (contingency table for ADR and DSS groups shown in **Table 2**). ADR prevalence was 4.44%. For those with ADR (+) and DSS < 0.2, OR was 3.12 (95% CI [1.07,8.03], p =0.018 for developing an ADR. The positive likelihood ratio (LR) was 2.59 [1.31-5.16]).

Discussion:

Drug ADRs are triggered by an undetermined balance of genetic and environmental factors. It is difficult to quantify the exact impact of genetic variation, as it may account for 20% to 95% of this variability. CA is a novel tool that attempts to elucidate the role of genetics by comprehensively incorporating both rare and common genetic variants in ADR prediction. The DSS's bimodal distribution generated by our algorithm is a novel and potentially useful tool to identify individuals at higher risk of ADR development. While the initial results do not clearly delineate those at risk, the positive trends reflected in the study show potential for the CA as a precision medicine tool to guide clinicians.

Study limitations include self-selection for UKB study participants, the inherent inaccuracies associated with registry data, including inconsistent ICD reporting for ADRs, and the small study numbers for ADR (+) group. Future analyses will include incorporating environmental factors that may contribute to ADR outcomes, and exploring other novel pharmacogenes involved in warfarin metabolism, and refining the CA with prospective clinical study datasets.

Table 1 UK Biobank study population demographics

Characteristic	Total	Female	Male
Patients, *n* (%)	630	217 (34.4)	413 (65.5)
Age, mean (SD), years	62 (6.4)	61 (6.7)	62 (6.2)
Weight, mean (SD), kg	87.1 (17.21)	79.1 (16.34)	91.5 (16.7)
Height, mean (SD), cm	172.4 (9.8)	162.9 (6.6)	177.3 (7.1)
Ethnicity, *n* (%)			
Caucasian	613 (96.9)	208 (95.8)	405 (98.1)
African	1 (0.13)	1 (0.46)	0 (0.0)
Caribbean	4 (0.5)	3 (1.38)	1 (0.24)
Asian	2 (0.25)	1 (0.46)	1 (0.24)
Others	10 (1.25)	4 (1.84)	6 (1.45)
ADR, n (%)	28	11 (39.3)	17 (60.7)

SD standard deviation
ADR adverse drug reaction

Table 1 demographics.png

Table 2 Contingency table for ADR and DSS

	DSS < 0.2	DSS ≥ 0.2	Total
ADR (+)	7	21	28
ADR (-)	58	544	602
Total	65	565	630

ADR adverse drug reaction
DSS drug safety score

Table 2 contingency table.png

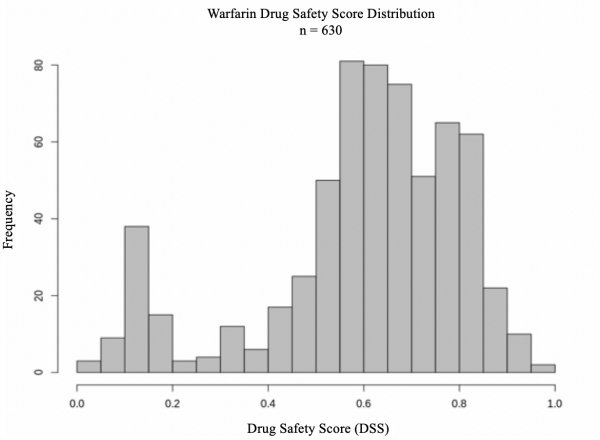


Figure 1 dss.png

Dendrimers from the bench to biotechs and towards the bedside

Friday, 21st February - 11:25: Oral Session: Emerging opportunities in personalized medicine, cutting-edge new strategies and solutions (Auditorium) - Plenary Speech - Abstract ID: 5

Dr. Anne-Marie Caminade [1], ***Dr. Jean-Pierre Majoral*** [1], ***Prof. Jean-Marie François*** [2], ***Dr. Richard Fabre*** [3], ***Dr. Serge Calet*** [4], ***Prof. Remy Poupot*** [5], ***Dr. Cédric-Olivier Turrin*** [1]

1. *LCC-CNRS, Toulouse,* ***2.*** *LISBP, UMR CNRS-INSA-INRA, Toulouse,* ***3.*** *Dendris, Labège,* ***4.*** *IMD-Pharma S.A.S., Toulouse,* ***5.*** *CPTP, INSERM-CNRS, Toulouse*

Dendrimers are hyper-branched synthetic macromolecules, which possess many properties, in particular for nanomedicine. The Figure displays the schematized structure of two generations (sizes) of dendrimers. Even if poor clinical translation has been observed up to now with dendrimers [1], a special class of dendrimers based on phosphorus as branching points are very promising [2]. Two biotech start-ups have been created, based on the phosphorus dendrimers technology.

DendrisTM [3] works in the field of multiplexing technology for the personalized in vitro diagnosis of pathogens [4], with healthcare impact in particular for respiratory diseases, sexual diseases, and breast cancer recurrence prognosis.

IMD-Pharma S.A.S [5] proposes a disruptive mode of action for the control of inflammation, in particular unmet medical needs in chronic inflammations, by modulating the activity of major cellular actors of the immune system [6,7].

[1] Svenson S., Chem. Soc. Rev. 2015, 44, 4131-4144

[2] Caminade A.M., Turrin C.O., Majoral J.P. (Eds) Phosphorus dendrimers in Biology and nanomedicine, Pan Stanford publishing, Singapore, 2018

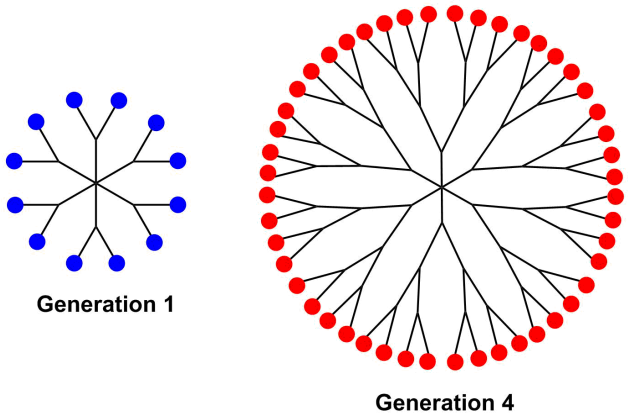
[3] https://www.dendris.fr/

[4] Majoral J.P., François J.M., Fabre R., Senescau A., Caminade A.M., Science China Mater. 2018, 61, 1454-1461.

[5] http://www.imd-pharma.com/

[6] 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; doi:10.1038/ncomms8722

[7] Fruchon S., Bellard E., Beton N., Goursat C., Oukhrib A., Caminade A.M., Blanzat M., Turrin C.O., Golzio M., Poupot R., Biomolecules, 2019, 9, 475; doi:10.3390/biom9090475



G1 et g4.png

openMTB: A System for Evidence-Driven Personalized Cancer Treatments in Molecular Tumor Boards

Friday, 21st February - 10:45: Oral Session: Integrating Big Data (Break-Out Room) - Oral - Abstract ID: 105

Dr. Irene Rui Chen [1], ***Ms. Bilge Sürün*** [2], ***Ms. Mirjam Figaschewski*** [3], ***Mr. Thorsten Tiede*** [4], ***Mr. Sebastian Winkler*** [5], ***Dr. Bryant Joseph Gilot*** [6], ***Dr. Eva-Maria Kobak*** [7], ***Prof. Oliver Kohlbacher*** [8]

1. *Institute for Translational Bioinformatics and 2 Institute for Bioinformatics and Medical Informatics,University of Tübingen & University Hospital Tübingen,* ***2.*** *Institute for Bioinformatics and Medical Informatics,,* ***3.*** *2 Institute for Bioinformatics and Medical Informatics, Tübingen, Germany, University of Tübingen, 72076 Tübingen, Germany 3 Dept. of Computer Science & Faculty of Medicine, University of Tübingen, 72076 Tübingen, Germany,* ***4.*** *Institute for Bioinformatics and Medical Informatics, Tübingen, Germany, University of Tübingen, 72076 Tübingen, Germany 3 Dept. of Computer Science & Faculty of Medicine, University of Tübingen, 72076 Tübingen, Germany,* ***5.*** *Institute for Translational Bioinformatics; Dept. of Computer Science & Faculty of MedicineUniversity of Tübingen & University Medical Center Tübingen,* ***6.*** *Institute of Translational Bioinformatics, University of Tübingen & University Hospital Tübingen, 72076 Tübingen, Germany 2 Institute for Bioinformatics and Medical Informatics, Tübingen, Germany, University of Tübingen, 72076 Tübingen, Germany,* ***7.*** *Institute of Translational Bioinformatics, University of Tübingen & University Hospital Tübingen, 72076 Tübingen, Germany,Institute for Bioinformatics and Medical Informatics, Tübingen, Germany, University of Tübingen, 72076 Tübingen, Germany,* ***8.*** *Applied Bioinformatics, Institute for Bioinformatics and Medical Informatics, Dept. of Computer Science, University of Tübingen; Institute for Translational Bioinformatics, University Hospital Tübingen*

Introduction

Cancer is a life-threatening disease, primarily caused by somatic genomic aberration. The mechanisms of carcinogenesis are individualized, therefore molecularly-targeted personalized therapies are needed. This has resulted in the establishment of multi-disciplinary Molecular Tumor Boards (MTBs) which discuss and evaluate patients' data with the goal of suggesting the most optimal therapies. The complexity of genomic data hinders its routine clinical usage in precision medicine, there is thus a need for integrated, automated, interactive visual analytics systems.

Our system, openMTB which enhances MTB workflows by enabling healthcare providers to access to all data relevant to therapeutic decisions. It engages diverse expertise by offering a virtual and digital platform besides regular face-to-face meetings.

Methods

OpenMTB consists of different components addressing different domains for the overall system refer to Fig1. To ensure we fully address health professionals' needs, a user - driven approach was conducted for the design and development from day one. In particular, a close interaction between the technical development team and the clinical oncologists has been engaged to focus on usability, comprehensiveness, quality of integrated data, and effectiveness of decision supports. The technical development team attended the clinical decision-making procedure to understand and observe the MTB processes regarding complex oncological cases. Questionnaires and interviews were used to formalize specific requirements, user cases, workflows as well as defining the functionalities for the system. An iterative design process was constantly used to improve these specifications based on the mock-ups through users' feedback. One of key components, Clinical Variant Annotation Pipeline(ClinVAP) according to Variant Annotation infrastructure in Fig2 was implemented to extract relevant information from simple somatic mutations(SNVs) of a patient and create structured clinical reports by annotating, prioritizing and filtering the genomic variants using various databases. Another key component BioGraphVisart has been developed to interactively visualize genes that are possibly related to a specific cancer or unknown target for drug treatment.

Results

Based on previous findings, the current prototype took the limitation of time constraints into the consideration and optimized the workflow into a three-phases including preparation, review and conference (demonstrated in Fig3). Our system improves the accuracy and efficiency for evidence-driven treatments and addresses the challenge of converting research-based software into clinical practice. It enables clinicians to (a) define patient cohorts based on a full semantic integration of clinical and HT data from aggregating five hospitals' patients data in Germany, b) incorporate the Clinical Variant Annotation Pipeline (ClinVAP) (c) construct gene regulatory networks(one example is shown in Fig3) to understand biological pathway and discuss rare cases in sufficient depth, d) integrate visual analytics by innovative digital analysis methods such as pattern recognition or artificial intelligence for intuitive data interpretation.

Discussion and Conclusion

OpenMTB is a large open-source software ecosystem closing the gap between bioinformatics research and healthcare. It answers the needs of MTBs by providing them with comprehensive and processed data, and benefits both patients and the clinicians. In the future, we aim to make the system transferrable to other molecularly mediated diseases to improve health care processes and decision support.

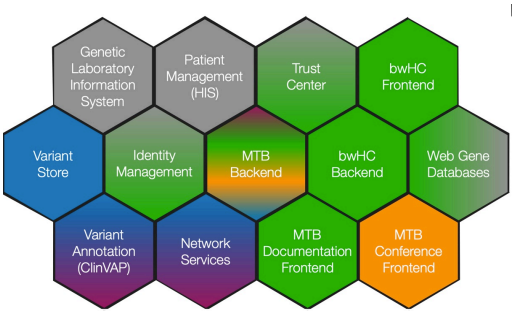


Fig1 domainoverview.jpg

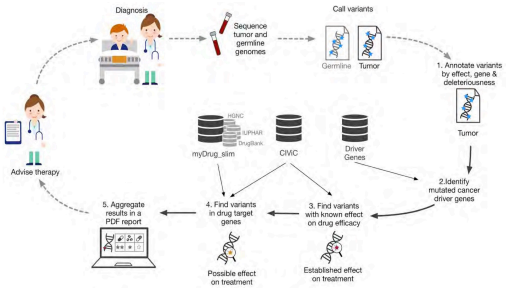


Fig2 infrastructure.jpg

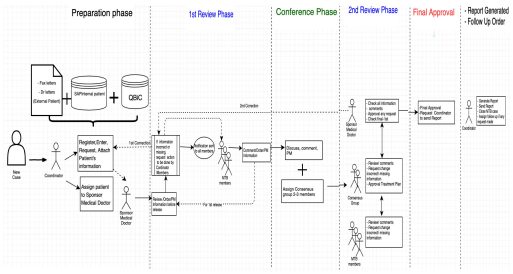


Fig3 workflow.jpg

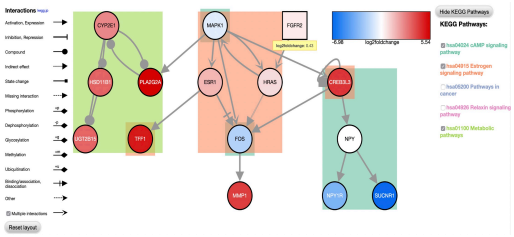


Fig4 genenetwork.jpg

Prescription drug use and related actionable drug-gene interactions in the Danish population

Friday, 21st February - 11:05: Oral Session: Integrating Big Data (Break-Out Room) - Oral - Abstract ID: 40

Dr. Carin Lunenburg [1], ***Dr. Alexander Hauser*** [2], ***Dr. Kazi Ishtiak-Ahmed*** [1], ***Dr. Christiane Gasse*** [1]

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Background:
Many commonly used drugs have great variability in drug metabolism and response. Pharmacogenetics (PGx) studies genetic variation linked to drug efficacy and adverse events, and aims to improve drug therapy using the individual patients' genetic make-up. 'Actionable PGx' refers to drugs, geno- or phenotypes for which literature-based dosing recommendations in PGx guidelines are provided. Little is known about the potential impact of actionable PGx on the population level, possibly hindering implementation of PGx in clinical care. Therefore, we investigated how many patients use actionable PGx drugs, have actionable geno- or phenotypes and which patients could benefit the most of PGx testing.
Methods:
We included PGx recommendations from two international PGx consortia (CPIC and DPWG) and identified all actionable PGx drugs. We extracted the number of users per actionable prescription PGx drug among the total Danish population in 2017 from public Danish prescription registries (MEDSTAT), stratified on sex and age. We estimated frequencies of actionable geno- or phenotypes (poor, intermediate, extensive and (ultra)rapid metabolizers; PM, IM, EM, UM, respectively) based on reported frequencies from literature. For each drug-gene interaction (DGI) we identified 1] the total number of drug users, 2] total estimated number of users with an actionable geno- or phenotype, 3] the estimated prevalence of actionable geno- or phenotypes (also per age group) and 4] sex ratio.
Results:
We mapped 68 actionable PGx drugs with their interacting genes and drug classes. Of these, 41 unique drugs (49 DGIs) were identified in prescription drug users in primary care in Denmark. The number of drug users varied from 10-341,395 users in 2017. The estimated median frequency of actionable geno- or phenotypes among prescription drug users was 25% (interquartile range: 7-26%). Six out of 41 drugs were used more than twice as much in females. Actionable PGx drugs were most frequently used by 45-79 years olds (62%), followed by 25-44 year olds (18%). Only 4% of the users of the included drugs was aged below 17 years. Almost half of the actionable PGx drugs (19/41) were psychotropics, i.e. antidepressants, antipsychotics or psychostimulants.
Conclusion:
PGx testing can have a substantial impact on the population, as one in four prescription drug users has an actionable geno- or phenotype for which a dose recommendation is provided. These patients could thus benefit from PGx testing, if followed by a dose adjustment to improve drug effectiveness and reduce the risk of adverse events. We advocate for prospective panel-based PGx testing at the time of the first PGx drug prescription ('as needed'), with PGx results ready to be applied prior to start of the first, and all future, therapies.

Pharmacogenetics of chemotherapy response in osteosarcoma: a genetic variant in SLC7A8 is associated with progressive disease

Friday, 21st February - 11:25: Oral Session: Integrating Big Data (Break-Out Room) - Oral - Abstract ID: 48

Ms. Evelien Hurkmans [1], ***Dr. Uta Flucke*** [1], ***Ms. Yvonne Versleijen-Jonkers*** [1], ***Mr. Jan Koenderink*** [1], ***Prof. Hans Gelderblom*** [2], ***Prof. Henk Jan Guchelaar*** [2], ***Dr. Rachael Windsor*** [3], ***Prof. Ana Patiño-Garcia*** [4], ***Ms. Anna González-Neira*** [5], ***Mr. Sumanth Nagabushan*** [6], ***Mr. Daniel Catchpoole*** [6], ***Mx. Collaborators of the GO-consortium*** [7], ***Dr. Maroeska te Loo*** [1], ***Dr. Marieke Coenen*** [1]

1. *Radboud university medical center, Nijmegen,* ***2.*** *Leiden University Medical Center, Leiden,* ***3.*** *University College Hospital, London,* ***4.*** *University Clinic of Navarra,* ***5.*** *Spanish National Cancer Research Center,* ***6.*** *The Children's Hospital at Westmead, Westmead, 7. multiple*

Introduction

Despite (neo)adjuvant chemotherapy in primary osteosarcoma, some patients progress during first-line systemic treatment and have a poor prognosis. In this study, we investigated whether patients with an inadequate response to treatment, defined as progressive disease, have a distinctive pharmacogenetic profile.

Methods

Progressive disease is defined as primary tumor and/or metastasis growth or formation within to 3 months after end of adjuvant chemotherapy or first-line treatment in case of primary metastatic disease; and/or inadequacy to reach complete remission at the end of therapy for primary localized or primary metastatic osteosarcoma. Germline DNA from 287 Dutch high-grade osteosarcoma patients treated with cisplatin and doxorubicin-based chemotherapy was genotyped using the DMET Plus array (containing 1,936 genetic markers in 231 drug metabolism and transporter genes). Associations between genetic variants and progressive disease were assessed using logistic regression models. Consequently, variants associated with progressive disease (P<0.05) were validated in independent cohorts of 146 (from Spain and UK) and 28 patients (from Australia). Genes that contain variants that were independently associated to progressive disease are subjected to functional studies. An immunohistochemistry staining was performed in osteosarcoma tissue from Dutch and Australian patients. Results are scored by 2 independent scorers and patients with >10% expression are considered positive for LAT2 expression. In addition, a HEK-293 cell model, overexpressing LAT2 (SLC7A8) and its heterodimer 4F2 (SLC3A2), was established to study the interaction of LAT2-4F2 with cisplatin, doxorubicin and methotrexate. The model was validated with (3H-)L-Alanine as a known substrate.

Results

In the association analyses of genetic variants and progressive disease, adjusted for the presence of primary metastases, sex and age at diagnosis, 10 genetic variants in 6 genes were associated (P<0.05) with progressive disease in the Dutch cohort. Of these, SLC7A8 rs1884545 and SLC7A8 rs8013529 were independently replicated in the validation cohort, and showed increased significance in meta-analysis of all cohorts combined (OR 0.22 [0.07-0.63], P=0.005 and OR 0.19 [0.06-0.55], P=0.002, resp.). SLC7A8 encodes for the L-type amino acid transporter 2 (LAT2). LAT2 expression in osteosarcoma tissue at diagnosis is not associated to progressive disease (p=0.172). However, all patients with LAT2 expression (n=9) survive after 5 years whereas only 67% of patients without LAT2 expression (n=34) survives after 5 years (p=0.082). The LAT2-4F2 overexpression model was validated with L-Alanine as a known substrate (Km = 598 µM (95% CI 304 – 892 µM). Cisplatin, doxorubicin or methotrexate did not significantly inhibit L-Alanine uptake.

Discussion

Two genetic variants in SLC7A8 are found to be protective of progressive disease in patients with osteosarcoma and these associations are validated in an independent patient cohort. SLC7A8 encodes for the L-type amino

acid transporter 2 (LAT2). Increased overall survival is suggested in the presence of LAT2 expression in tumor tissue at diagnosis. Furthermore, an in vitro model is ongoing to assess interactions of cisplatin, doxorubicin or methotrexate with this transporter. These results will provide new evidence that could give new opportunities to improve treatment of osteosarcoma patients.

Liquid biopsy in the era precision medicine

Friday, 21st February - 13:30: Plenary Speeches: Precision Medecine and Translational Technologies (Auditorium) - Plenary Speech - Abstract ID: 139

Prof. Klaus Pantel [1]

1. *UKE University Medical Center Hamburg-Eppendorf*

Coming soon

Systemic standardized metabolic phenotyping of mouse models: perspectives for precision medicine

Friday, 21st February - 14:00: Plenary Speeches: Precision Medecine and Translational Technologies (Auditorium) - Plenary Speech - Abstract ID: 140

Prof. Martin Hrabe de Angelis [1]

1. *Helmholtz Zentrum München, Munich*

Coming soon

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