PEMED 2021

Personalized and Precision Medicine

International Conference

April 7-9 | ONLINE

BOOK OF ABSTRACT

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High dose Vitamin C and inactivation of DNA repair boost cancer immunotherapy

Wednesday, 7th April - 09:10: Plenary 1 (Main Room) - Oral - Abstract ID: 79

Prof. Alberto Bardelli [1]

1. *University of Turin - Dept of Oncology*

Vitamin C (VitC) is known to directly impair cancer cell growth in preclinical models but there is little clinical evidence on its anti-tumoral efficacy. Additionally, whether and how VitC modulates anticancer immune responses is mostly unknown. We find that a fully competent immune system is required to maximize the anti-proliferative effect of VitC in breast, colorectal, melanoma and pancreatic murine tumors. High-dose VitC modulates infiltration of the tumor microenvironment by cells of the immune system and delays cancer growth in a T cell-dependent manner. Not only does VitC enhance the cytotoxic activity of adoptively transferred CD8 T cells, but it also co-operates with immune checkpoint therapy (ICT) in several cancer types. Combination of VitC and ICT can be curative in models of mismatch repair deficient tumors with high mutational burden. Our work provides the rationale for clinical trials combining ICT with high doses of VitC.

TBD

Wednesday, 7th April - 09:45: Plenary 1 (Main Room) - Oral - Abstract ID: 90

Mr. Aslaug Helland [1]

1. *unknown*

TBD

TBD

Wednesday, 7th April - 10:20: Plenary 1 (Main Room) - Oral - Abstract ID: 91

Mr. Hege Russnes [1]

1. *unknown*

TBD

Epigenetics and Epitranscriptomics of Human Cancer: From Knowledge to Applications

Wednesday, 7th April - 11:15: Plenary 2 (Main Room) - Oral - Abstract ID: 93

Prof. Manel Esteller [1]

1. *University of Barcelona*

TBD

TBD

Wednesday, 7th April - 11:50: Plenary 2 (Main Room) - Oral - Abstract ID: 92

Mr. Stephan Pfister [1]

1. *unknown*

TBD

A novel synthetic lethal strategy: targeting DNA damage repair based on epigenetic defects

Wednesday, 7th April - 13:30: Plenary 3 (Main Room) - Oral - Abstract ID: 74

Prof. Mingzhou Guo [1]

1. *Chinese PLA General Hospital*

DNA methylation is the most useful epigenetic marker for human disease studies because it is stable. Aberrant DNA methylation has been reported in genes involved in cell cycle, DNA damage repair (DDR), Wnt, PI3K-Akt-mTOR and NF-κB pathways. DDR deficient cancers become critically dependent on backup DNA repair pathways. With greater understanding of the biology of DDR, small molecules are being developed as new anticancer therapies by targeting DDR. Understanding the causative epigenetic changes of "loss of function" may develop novel therapeutic strategies in cancer. Our recent study found that RASSF10 is methylated in 42.6%（43/101）of esophageal dysplasia and 71.8%（718/1000）of esophageal cancer. RASSF10 suppresses esophageal cancer growth both *in vitro* and *in vivo* by inhibiting Wnt signaling. RASSF10 methylation is a synthetic lethal marker for XAV939 (a Wnt signaling inhibitor) and BMN673(a PARP inhibitor). Another study found that NRN1 is frequently methylated in human esophageal cancer and the expression of NRN1 is regulated by promoter region methylation. NRN1 methylation is an independent prognostic factor for poor 5-year overall survival in ESCC. NRN1 suppresses esophageal cancer cell growth by inhibiting PI3K-Akt-mTOR signaling both *in vitro* and *in vivo*. Methylation of NRN1 is a novel prognostic marker of synergistic lethal therapy in combination with NVP-BEZ235 (PI3K inhibitor) and VE-822 (an ATR inhibitor). We also found that methylation of TMEM176A is a potential diagnostic marker and a novel synthetic lethal therapeutic marker for AZD0156 (an ATM inhibitor) in human lung cancer.

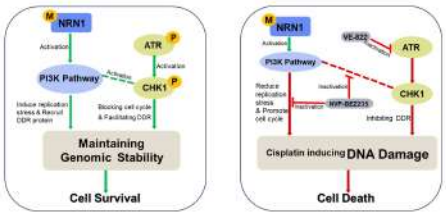

Fig 1.jpg

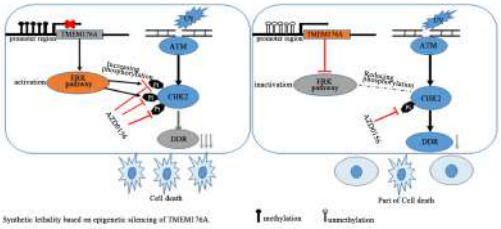

Fig 2.jpg

Determinants of immunological evasion and immune checkpoint inhibition response: the genetic front

Wednesday, 7th April - 14:05: Plenary 3 (Main Room) - Oral - Abstract ID: 69

Dr. Montse Sanchez-Cespedes [1]

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

Introduction: For its development, a cancer cell has to acquire a variety of capabilities, including avoiding host immune surveillance. The immune system is capable of recognizing non-self-antigens presented by cancer cells and, eventually, eliminating them. However, to preclude the action of the immune system, some cancers develop immunotolerance which implies avoiding or bypassing T-cell recognition and function. On the other hand, over the past several years, immune checkpoint inhibitors (ICIs) have begun to transform clinical cancer care, including lung cancer (LC), the most lethal type of cancer worldwide. However, despite its unquestionable benefits, to take full advantage of the therapeutic possibilities of ICIs, accurate predictive markers to faithfully select patients that will respond to ICIs are still needed. Moreover, the molecular basis underlying the extraordinary capability of evading the immune system of small cell lung cancer (SCLC), a highly aggressive type of LC, need to be understood. Methods: An integrative project has been undertaken using wide genomic sequencing technologies and involving clinical and preclinical scientists to identify novel markers that help predicting response or resistance to ICIs in LC. Results: In this talk, it will be described our findings about the dynamic interaction between the cancer cell and the immune system during carcinogenesis, with a particular focus on the functions and gene alterations that prevent the host immunoresponse in LC. Special emphasis will be dedicated to the description of the deleterious gene alterations in components of the major histocompatibility complex (HLA-I or B2M) and of the response to IFNγ (such as JAK2). Alterations at these two pathways are mutually exclusive and can affect up to one fifth of the LCs. The participation of other gene alterations, such as those of common oncogenes and tumor suppressors, and of the epigenetic alterations will also be explained, in detail. Finally, the potential use of the tumor's genetic profile to predict sensitivity to ICIs will also be discussed.

TBD

Wednesday, 7th April - 15:00: Plenary 4 (Main Room) - Oral - Abstract ID: 94

Mr. Qian Zhang [1]

1. *State Key Laboratory of Alternate Electrical Power System with Renewable Energy Sources North China Electric Power University, Beijing, China*

TBD

TBD

Wednesday, 7th April - 15:35: Plenary 4 (Main Room) - Oral - Abstract ID: 95

Dr. Elaine Jaffe [1]

1. *National Cancer Institute*

TBD

TBD

Wednesday, 7th April - 16:10: Plenary 4 (Main Room) - Oral - Abstract ID: 96

Mr. Ari Melnick [1]

1. *unknown*

TBD

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Thursday, 8th April - 09:00: Plenary 1 (Main Room) - Oral - Abstract ID: 97

Prof. Ann Daly [1]

1. *New*

TBD

TBD

Thursday, 8th April - 09:35: Plenary 1 (Main Room) - Oral - Abstract ID: 100

Prof. Matthias Schwab [1]

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

TBD

Dendrimers: emerging opportunities for bioimaging and diagnosis

Thursday, 8th April - 10:30: Plenary 2 (Main Room) - Oral - Abstract ID: 88

Dr. Anne-Marie Caminade [1]

1. *LCC-CNRS*

Dendrimers are perfectly defined hyperbranched macromolecules, which possess many properties, in particular for nanomedicine [1,2]. This talk will give an overview on the use of dendrimers for bioimaging and diagnosis *in vivo*, and how this topic could open opportunities in personalized and precision medicine. Emphasis will be essentially on magnetic resonance imaging (MRI) contrast agents, mostly based on gadolinium complexes, and radioactive dendrimer complexes for single photon emission computed tomography (SPECT), mainly with technetium (^{99m}Tc), and also for positron emission tomography (PET), mainly with indium (^{111}In) and gallium (^{68}Ga) [3].

[1] Rolland O., Turrin C.O., Caminade A.M., Majoral J.P. “Dendrimers and nanomedicine: Multivalency in action”. *New. J. Chem.* **2009**, *33*, 1809-1824.

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

[3] Caminade A.M., Hameau A., Turrin C.O., Laurent R., Majoral J.P. “Dendritic metal complexes for bioimaging. Recent advances”. *Coord. Chem. Rev.* **2021**, *430*, 213739.

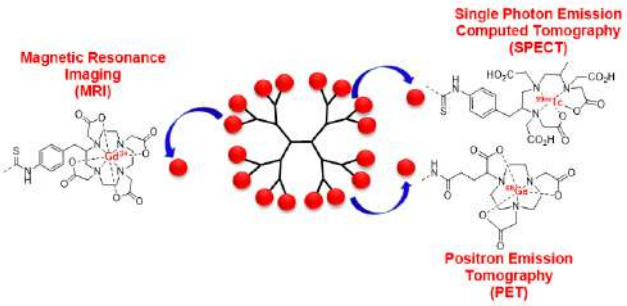

Figure pemed 2021.png

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Thursday, 8th April - 11:05: Plenary 2 (Main Room) - Oral - Abstract ID: 99

Mr. Kari Stefansson [1]

1. *deCODE Genetics*

TBD

TBD

Thursday, 8th April - 13:00: Plenary 3 (Main Room) - Oral - Abstract ID: 101

Mr. Julio Saez-Rodriguez [1]

1. *unknown*

TBD

TBD

Thursday, 8th April - 13:35: Plenary 3 (Main Room) - Oral - Abstract ID: 102

Mr. Eduard Porta [1]

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

TBD

TBD

Thursday, 8th April - 14:10: Plenary 3 (Main Room) - Oral - Abstract ID: 103

Mr. Emmanouil Dermitzakis [1]

1. *unknown*

TBD

TBD

Thursday, 8th April - 15:05: Plenary 4 (Main Room) - Oral - Abstract ID: 104

Mr. Amos Tanay [1]

1. *unknown*

TBD

TBD

Thursday, 8th April - 15:40: Plenary 4 (Main Room) - Oral - Abstract ID: 105

Dr. Olivier Elemento [1]

1. *Caryl and Israel Englander Institute for Precision Medicine*

TBD

TBD

Friday, 9th April - 09:00: Plenary 1 (Main Room) - Oral - Abstract ID: 106

Prof. Maria Alonso [1]

1. *University of Santiago de Compostela*

TBD

TBD

Friday, 9th April - 09:35: Plenary 1 (Main Room) - Oral - Abstract ID: 107

Ms. Julia Blanco [1]

1. *unknown*

TBD

TBD

Friday, 9th April - 10:10: Plenary 1 (Main Room) - Oral - Abstract ID: 108

Mr. Paul Bastard [1]

1. *unknown*

TBD

Pharmacogenetic genotype and phenotype frequencies and drug utilization patterns in a large Danish population-based case-cohort sample for psychiatric research

Friday, 9th April - 11:05: Oral Session 1 (Main Room) - Oral - Abstract ID: 75

Dr. Christiane Gasse [1], ***Dr. Janne Thirstrup*** [2], ***Mr. Jonas Bybjerg-Grauholm*** [3], ***Dr. Marie Bækvad-Hansen*** [3], ***Prof. David M. Hougaard*** [4], ***Prof. Merete Nordentoft*** [5], ***Prof. Thomas Werge*** [6], ***Prof. Anders Børglum*** [7], ***Prof. Ole Mors*** [1], ***Prof. Preben B. Mortensen*** [8], ***Dr. Kazi Ishtiak Ahmed*** [9], ***Dr. Carin Lunenenburg*** [9]

1. *Psychosis Research Unit, Aarhus University Hospital Psychiatry, Aarhus,* ***2.*** *Department of Clinical Medicine, Aarhus University, Aarhus,* ***3.*** *Danish Center for Neonatal Screening, Statens Serum Institut, Copenhagen,* ***4.*** *The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus/Copenhagen,* ***5.*** *Mental Health Centre Copenhagen, Capital Region of Denmark, Copenhagen University Hospital, Copenhagen,* ***6.*** *Institute of Biological Psychiatry, Mental Health Services, Copenhagen University, Copenhagen,* ***7.*** *Center for Genomics and Personalized Medicine, Aarhus University, Aarhus,* ***8.*** *NCRR National Centre for Register-Based Research, School of Business and Social Sciences, Aarhus University, Aarhus,* ***9.*** *Department of Affective Disorders, Aarhus University Hospital Psychiatry, Aarhus*

Background: Large unselected population-based genetic and drug data could improve our current understanding of pharmacogenetics (PGx) based on selected populations. Here, we investigated pharmacogenetic frequencies of genotypes and phenotypes of a large Danish population-based case-cohort sample (iPSYCH2012; data of the Integrative Psychiatric Research consortium) and the drug utilization pattern of 69 actionable PGx drugs as defined by international PGx consortia.

Methods: We used genetic and register-based information of 77 684 singleton born individuals in Denmark between 1981-2005, of whom 51 464 had a psychiatric hospital-based diagnosis of a mental disorder of ADHD, autism, affective disorders, or schizophrenia (MD case cohort), and of 26 220 randomly selected individuals from the Danish population (population cohort). We searched array-based genotype data imputed to 8.4 million genetic variants for a selected pharmacogenetic panel of 42 clinically relevant variants and a *CYP2D6*gene deletion and duplication. Prescription data since 1995-2016 was linked to the cohorts to identify (life-time) incident use of 69 actionable PGx drugs.

Results: We identified 19 of 42 PGx variants. Minor allele frequencies (MAFs) were consistent with previously reported MAFs, and did not differ between MD case- and population cohorts. Almost all individuals carried at least one mutant allele (>99.9%), 87% carried three or more mutant alleles. Translated into phenotypes, >99.9% of individuals had at least one divergent phenotype, e.g. extensive metabolizer. Combining CYP2C19-CYP2D6 phenotypes revealed 72.7% of individuals having divergent phenotypes for one or both enzymes. Of the 69 PGx drugs, 39 had been redeemed on prescriptions by the study population by the age of 38 years. Psychotropics metabolized by CYP2C19 or CYP2D6 accounted for almost half of the PGx drugs. The most frequently used PGx drugs were estrogens, weak opioids, proton-pump inhibitors and antidepressants across most cohorts. The use of at least 1 PGx drug varied from 23.1% in population males to 97.2% in females with schizophrenia. Males with ADHD or autism were the youngest first-time PGx drug users at a mean of 11.6 years. The mean number of different PGx drugs varied from 1.2 in male population individuals to 5.6 in individuals with schizophrenia. The prevalence of different PGx drugs linked to more than one gene varied between 25.3% in males of the population to 94.1% in females with schizophrenia.

Conclusions: Panel-based PGx testing could contribute to treatment decisions, in particular in individuals with MD and females, due to high numbers of individuals with at least one mutant allele in a pharmacogenetic variant or divergent phenotype and frequent use of psychotropic drugs from a young age.

Impact of POR knockdown on hepatic gene expression in HepaRG cells

Friday, 9th April - 11:20: Oral Session 1 (Main Room) - Oral - Abstract ID: 76

Ms. Tamara Heintze [1], ***Dr. Kathrin Klein*** [1], ***Dr. Ute Hofmann*** [1], ***Ms. Denise Wilhelm*** [1], ***Prof. Matthias Schwab*** [1], ***Dr. Ulrich Zanger*** [1]

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

Background: Cytochrome P450 reductase (POR) is a ubiquitous microsomal electron transport protein essential to cytochrome P450 (CYP) - mediated biosynthesis of endogenous substrances like bile acids and other steroids as well as for oxidative metabolism of xenobiotics. In humans, certain POR mutations lead to deficient POR (PORD), which is characterized by a broad phenotypic spectrum including cortisol deficiency, altered sex steroid synthesis, disorders of sex development and skeletal malformations resembling the Antley-Bixler syndrome phenotype. While effects of diminished Por were extensively studied in mouse models, studies in human models are lacking. Using CRISPR/Cas9 technology we recently established two genetic HepaRG *POR* knockout cell lines (Heintze et al., Sci Rep. 2021, PMID: 33509243). Here we studied the effect of diminished POR levels on drug metabolizing CYPs, as well as on other endogenous pathways.

Methods: Using lentiviral particles, Cas9 and two single guide RNAs (sgRNAs) targeting human *POR*were delivered into HepaRG cells. *POR* knockout was evaluated by immunoblotting, 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 seven CYP enzymes of families 1, 2 and 3. Excreted bile acids were quantified in the cell medium by negative electrospray (ESI) liquid chromatography tandem mass spectrometry (LC-MS/MS). Quantification of mRNA panels representing various gene classes was performed by qPCR (Fluidigm). Protein expression was assessed by LC-MS/MS analysis.

Results:*POR* gene disruption in HepaRG cells resulted in POR knockdown of protein and mRNA by 60 to 80 %. This led to variably decreased CYP activities ranging from 30 % (CYP2C8) up to 95 % (CYP2C9). Further, POR knockdown resulted in deregulated bile acid synthesis. While secretion of cholic acid derivates was strongly decreased, secretion of chenodeoxycholic acid derivates were increased. POR knockdown also had differential effects on mRNA expression, in particular a general downregulation of transcriptional regulators of drug metabolism, upregulation of certain CYPs (e.g. CYPs 1A1/2) and downregulation of others (e.g. CYPs 2E1, 2C9). Protein expression data showed the influence of diminished POR on the expression of enzymes involved in bile acid and cholesterol synthesis.

Conclusion: The HepaRG *POR* knockout cells give us the possibility to further investigate the regulatory mechanisms and functional impact of POR on CYPs as well as other endogenous pathways. These CRISPR/Cas9 generated cell lines can now be used for knockout studies of other genes.

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

Ex vivo culture of human tissue slices as a predictive preclinical model to evaluate drug efficiency for patients with ovarian cancer

Friday, 9th April - 11:35: Oral Session 1 (Main Room) - Oral - Abstract ID: 78

Dr. Meng Dong [1], ***Ms. Kathrin Böpple*** [1], ***Dr. Bernd Winkler*** [2], ***Dr. Chunguang Liang*** [3], ***Dr. Frank Essmann*** [1], ***Prof. Walter E. Aulitzky*** [4]

1. *Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology and University of Tuebingen,* ***2.*** *Department of Gynaecology and Obstetrics, Robert Bosch Hospital,* ***3.*** *Bioinformatics, Biocenter, University of Würzburg,* ***4.*** *Department of Oncology, Robert Bosch Hospital*

Ovarian cancer is the major cause of death among women with gynecological cancers. It is a heterogeneous disease usually diagnosed at late stage and progresses rapidly. The standard therapy for ovarian cancer is resection of the affected tissue, followed by chemotherapy. However, patients frequently suffer from relapse of the disease and have adverse clinical outcomes. The lack of good preclinical models that can predict the efficacy of drugs in each patient is one of the major hurdles.

For personalized medicine it is crucial that the model captures the complex tumor biology *in vitro* in order to individually predict *in vivo* therapy of tumors. Precision-cut cancer tissue slices (PCCTS) maintain intra-tumor heterogeneity with regard to different cell types and preserved native microenvironment. Commonly, PCCTS are cultured statically on a filter support at an air-liquid interface which gives rise to intra-slice gradients during culture. We overcame this problem with the newly developed perfusion air culture (PAC) system which can offer continuous and precisely controlled oxygen, medium and drug supply.

The PCCTS from primary human ovarian tumors (phOVT) cultured in PAC system maintain the morphology, cell proliferation and microenvironment after 8 days cultivation. To analyze therapy response, Cisplatin was applied to PCCTS for 3 days. Cisplatin treatment was accompanied by minor increase of ɣ-H2AX while different patients showed diverse increase of cleavage of caspase-3 and PD-L1 expression indicating the heterogenous response of each patient to the drug treatment. The ovarian tumor resection and ascites single-cell RNA-seq data from the database were used to perform the CIBERSORTx deconvolution method to estimate the cell type composition in phOVT tumor tissue and tissue slices after culture or drug treatment from phOVT tissue RNA-seq data. The immune cell composition results from CIBERSORTx showed very good correlations with the immunohistochemistry (IHC) staining results from the phOVT tissues indicating that it is possible to infer the immune, tumor, and stromal cell content of the phOVT tissue slices after drug treatment from the bulk gene expression profile. By taking cellular composition into account, we can link the cellular characteristics and cellular content with treatment response.

In conclusion, cultivation of phOVT tissue slices provides an *ex vivo* model that preserves tumor heterogeneity and microenvironment which allows long-term culture of tumor tissue and analysis of therapy response - including immune therapy. It can be used as a predictive preclinical model to perform patient-specific *ex vivo* tests and thus allows personalized therapy adaption.

Machine learning characterization of psychiatric comorbidities in a rare disorder

Friday, 9th April - 11:50: Oral Session 1 (Main Room) - Oral - Abstract ID: 87

Dr. Seoho Song [1], ***Mr. Frederick Burton III*** [1], ***Mr. Soo Hwan Park*** [1], ***Dr. Deirdre Caffrey*** [2], ***Dr. Cybèle Arsan*** [3]

1. *Geisel School of Medicine, Dartmouth College,* ***2.*** *Columbia University Irving Medical Center,* ***3.*** *LAC+USC Medical Center*

Background:
Stiff person syndrome (SPS) is a rare neurologic disorder with characteristic muscle spasms and painful rigidity. While psychiatric comorbidities are suspected, a decisive link has yet to be established.
Objective:
This retrospective cohort study aimed to identify features in patients' past medical histories that identify SPS.
Methods:
322 past medical history items from 23 patients carrying SPS diagnoses and 25 controls, all anti-GAD positive, were vectorized as binary features. Using only features present in 4 or more patients (27 features), we generated a support vector machine (SVM) model using a Gaussian radial basis function kernel with inputs randomly split into training and test groups following a repeated stratified, 2-fold cross-validation scheme over 40 iterations, and feature importance assessed on the aggregate results. Features with the highest permutation importance scores were isolated as inputs for an optimized SVM model following the iterative algorithm. Feature importance analysis was performed on the aggregate results.
Results:
The initial list of 322 features was filtered, only including those present in 4 or more patients. The relative contribution of each feature to the model's architecture was computed via the permutation importance, and the model's accuracy and AUC were calibrated by calculating changes following progressive additions of each feature (from highest to lowest performance enhancing). Performance indices were maximized using 8 features: depression, dysphagia, joint pain, dyslipidemia, gastroesophageal reflux disease, headache, anxiety, hypothyroidism; highest to lowest importance. Performance metrics of the final model were as follows: accuracy 0.81 (CI_{95}[0.66-0.96]), AUC 0.84 (CI_{95}[0.70-0.98]), precision 0.85 (CI_{95}[0.72-0.96]), recall 0.74 (CI_{95}[0.58-0.90]), and F_1 0.78 (CI_{95}[0.62-0.94]).
Conclusion:
The final model classified SPS with an 81% accuracy based only on patients' past medical histories and ranked depression and anxiety as important predictors. This highlights SPS' association with psychiatric conditions and warrants an in-depth exploration for possible pathophysiological connections. Our approach serves as a proof-of-principle that data mining via machine learning can uncover value from passively collected - otherwise under-utilized - data in electronic health records. In this manner, machine learning can empower standard hypothesis-driven investigations, together forming a powerful, closed loop model for translational research.

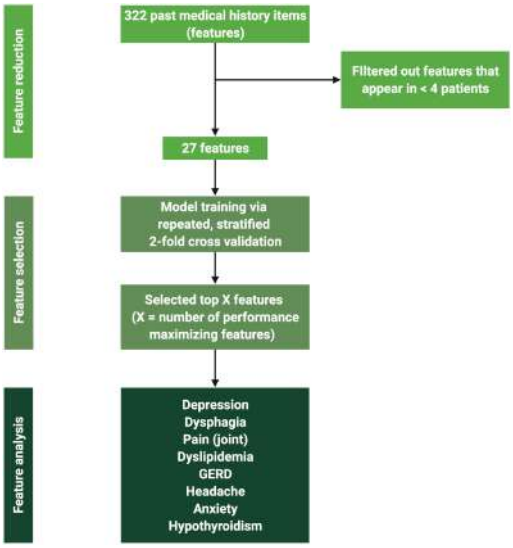

Figure 1. flow diagram of svm model.png

Table 1: Baseline demographic and clinical characteristics

	SPS+ Cohort (N = 23)	SPS- Cohort (N = 25)	*p*-value
Baseline Demographic Characteristics			
Age – years, mean (SD)	54.3 (10.7)	45.9 (21.6)	0.090
Female sex – no./total no. (%)	13/23 (56.5%)	12/25 (48.0%)	0.578
White ethnicity – no./total no. (%)	18/23 (78.3%)	18/25 (72.0%)	0.743
Clinical Characteristics			
Anti-GAD65 titer (serum) – nmol/L, mean (SD)	161.7 (521.1)	93.8 (299.1)	0.588
Trauma/stress-related disorders – no./total no. (%)	4/23 (17.4%)	2/25 (8.0%)	0.407
Anxiety disorders – no./total no. (%)	9/23 (39.1%)	7/25 (28.0%)	0.543
Schizophrenia spectrum and other psychotic disorders – no./total no. (%)	4/23 (17.4%)	1/25 (4.0%)	0.180
Depressive disorders – no./total no. (%)	12/23 (52.2%)	7/25 (28.0%)	0.140
Bipolar disorder and bipolar related disorders – no./total no. (%)	2/23 (8.7%)	0/25 (0.0%)	0.224
Obsessive-compulsive and related disorders – no./total no. (%)	2/23 (8.7%)	0/25 (0.0%)	0.224
Personality disorders – no./total no. (%)	3/23 (13.0%)	0/25 (0.0%)	0.102
Somatic symptom disorders – no./total no. (%)	3/23 (13.0%)	0/25 (0.0%)	0.102

Statistical differences were computed via Welch's t-tests or Fisher's exact tests.

Table 1. baseline demographic and clinical characteristics.png

Table 2: Performance indices of SVM model

	Mean	95% Confidence Interval	
		Lower Bound	Upper Bound
Accuracy = $\frac{TP+TN}{TP+TN+FP+FN}$	0.81	0.66	0.96
Area under curve (receiver operating characteristic)	0.84	0.70	0.98
Specificity = $\frac{TN}{TN+FP}$	0.86	0.74	0.98
Sensitivity (Recall) = $\frac{TP}{TP+FN}$	0.74	0.58	0.90
PPV (Precision) = $\frac{TP}{TP+FP}$	0.85	0.72	0.98
$F_1 = 2 \cdot \frac{precision \cdot recall}{precision+recall}$	0.78	0.62	0.94

Table 2. performance indices of svm model.png

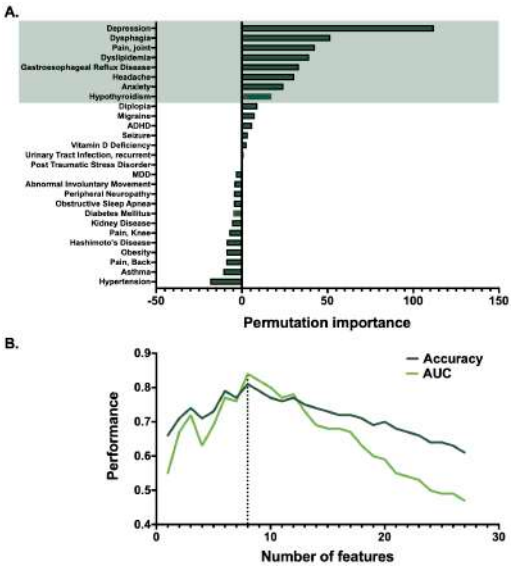

Figure 2. permutation feature importance.png

Assessment of circulating metabolites and microbiota-associated molecules in subjects with lean and obese NAFLD

Friday, 9th April - 12:05: Oral Session 1 (Main Room) - Oral - Abstract ID: 66

Dr. Mathias Haag [1], ***Dr. Stefan Winter*** [1], ***Ms. Julia Tevini*** [2], ***Dr. Alexandra Feldman*** [3], ***Dr. Sebastian Eder*** [3], ***Dr. Thomas Felder*** [2], ***Prof. Christian Datz*** [4], ***Ms. Enni-Kaisa Mustonen*** [1], ***Dr. Gerhard Liebisch*** [5], ***Dr. Oliver Burk*** [1], ***Prof. Bernhard Paulweber*** [6], ***Prof. Matthias Schwab*** [1], ***Prof. Elmar Aigner*** [3]

1. *Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart,* ***2.*** *Department of Laboratory Medicine, Paracelsus Medical University Salzburg,* ***3.*** *First Department of Medicine, Paracelsus Medical University, Salzburg,* ***4.*** *Department of Internal Medicine, Hospital Oberndorf,* ***5.*** *Institute of Clinical Chemistry and Laboratory Medicine, Regensburg University Hospital, Regensburg,* ***6.*** *First Department of Medicine, Paracelsus Medical University, Salzburg, Austria*

Introduction: Alterations in circulating metabolites have been described for obese non-alcoholic fatty liver disease (NAFLD). However, knowledge about changes related to molecules produced by the gut microbiome and a potential contribution of gender and body mass index (BMI) is limited. We aimed to investigate associations of serum metabolites, including microbiota-associated bile acids (BAs) and short chain fatty acids (SCFAs), in subjects with lean and obese NAFLD.

Methods:A subset of 204 subjects, recruited from the Salzburg Colon Cancer Prevention Initiative (SAKKOPI) study, were allocated to four groups: lean healthy (n=61), lean steatosis (n=49), obese healthy (n=47) and obese steatosis (n=47). The serum metabolome was assessed using the Metabolomics AbsoluteIDQ p180 kit (BIOCRATES Life Sciences). Serum BAs and SCFAs were quantified by independent, targeted LC/MS assays. Univariate and multivariate statistical analysis was performed with the R software.

Results: Significant positive associations of phosphatidylcholine species (e.g. PC 40:3) as well as specific amino acids (e.g. lysine and arginine) were evident for NAFLD independent of BMI and gender. Other amino acids (e.g. branched-chain amino acids leucine and isoleucine) were associated with gender only. The microbial metabolites propionate and iso-butyrate exhibited a strong interaction with lean steatosis and were found significantly elevated in the serum of male as well as female subjects. Unconjugated, secondary BAs deoxycholate (DCA) and ursodeoxycholate (UDCA) exhibited higher serum level in obese males independent of NAFLD while DCA was the sole BA species significantly elevated in lean NAFLD males. Considering a subset of n=11 metabolites (including microbiome-derived SCFAs), gender and BMI, resulted in median area under the curve of 0.86 for NAFLD prediction, based on a random forest approach with 5-fold nested cross-validation. *In vitro* follow up experiments in primary human hepatocytes revealed unaltered signaling of the farnesoid X receptor (FXR) upon DCA treatment.

Discussion: Lean NAFLD subjects were characterized by elevated blood amounts of SCFAs compared to lean healthy people irrespective of gender. Our analysis revealed subtle gender-specific differences for secondary, unconjugated BAs that were rather related to body weight than steatosis hence indicating a complex interplay between dysbiosis, liver metabolic function and circulating metabolites. Further studies in independent clinical cohorts are warranted to confirm these preliminary findings and to assess a potential diagnostic value of microbial metabolites for personalized NAFLD therapy.

Development of DNA-biochip for detection of mutations in rpoB, embB and inhA genes in Mycobacterium tuberculosis clinical isolates.

Friday, 9th April - 12:20: Oral Session 1 (Main Room) - Oral - Abstract ID: 58

Dr. Bharti Jain [1], ***Dr. Savita Kulkarni*** [1]

1. *Bhabha Atomic Research Centre*

*Introduction:Mycobacterium tuberculosis (M.Tb)*is a leading cause of death worldwide. In drug resistant tuberculosis, infectiousness is prolonged, jeopardizing efforts to control TB. The conventional tuberculosis drug susceptibility tests (DST) are sensitive and specific, but not rapid. DNA sequencing is most reliable and accurate method but expensive. Therefore, a molecular approach was developed to identify drug-resistant strains of *M.Tb* by means of DNA-biochips with oligonucleotides immobilized on highly microporous polycarbonate track-etched membranes (PC-TEM) as a novel support. Our aim was to design and develop a sensitive and specific chemiluminescence based biochip assay to detect mutations in the rifampicin resistance determining region (RRDR) of *rpoB* associated with rifampicin (RMP) resistance and loci in *inhA* and *embB* genes associated with isoniazid (INH) and ethambutol (EMB) resistance respectively.

Methods: DNA-biochip was prepared by immobilizing 15 specific probes designed to detect mutations in *rpoB, embB andinhA* genes on glutaraldehyde activated PC-TEM (Fig 1and 2). The mutations tested were at codon 516, 526, 531 and 533 (common mutation sites) for RMP, *inhA-15* (C-T) mutation for INH and codon 306 for EMB resistance (Fig.2). Fifty culture isolates were used to evaluate the ability of in-house developed biochip to detect the mutations. A multiplex PCR was developed to amplify the specific regions of *rpoB, embB*and*inhA*genes. This was followed by hybridization of PCR products with DNA-biochip. Chemiluminescence was used for signal detection. The DNA biochip assay conditions were optimized following analysis of samples with known mutations. The accuracy of DNA-biochip was determined by comparing its results with DST.

Results: Dark and distinct spots with clear interpretable images were obtained on biochips using chemiluminescence imager (Fig.3). Out of 45 amplified isolates, 37.7% show wild type sequences, 53.3% of samples were monoresistance showing resistance to either rifampicin, isoniazid or ethambutol. 4.4% samples were polydrug resistance showing mutation inboth *rpoB* gene and *embB* genes while 4.4% were MDR, harboring mutation in *rpoB* and *inhA* genes. The results are in complete agreement with DST results.

Discussion: We have shown the use of PC-TEMs for developing DNA chip for detection of mutations associated with RMP, INH and EMB resistance. Developed DNA-biochip was able to clearly and accurately detect the different mutations present in the samples and thus provides detailed and reliable data for clinical diagnosis and is well suited for testing the mutations in *rpoB, inhA*and*embB*genes.

Probe name	Gene-probe	Sequence
rpoB 1	rpoB 514-520 WT	TTCATGGACCAGAACAACCCG
rpoB 2	rpoB 521-525 WT	CTGTCGGGGTTGACC
rpoB 3	rpoB 524-529 WT	TTGACCCACAAGCVGCCGA
rpoB 4	rpoB 530-534 WT	CTGTCGGCGCTGGGG
rpoB 5	rpoB 531 -TTG	CTGTTGGCGCTGGGG
rpoB 6	rpoB 531 -TGG	CTGTGGGCGCTGGGG
rpoB 7	rpoB 533-CCG	GCGCCGGGGCCC
rpoB 8	rpoB 526 -TAC	TTGACCTACAAGCGCCGA
rpoB 9	rpoB 526 -GAC	TTGACCGACAAGCGCCGA
rpoB 10	rpoB 516 -TAC	TTCATGTACCAGAAC
inhA 1	inhA: -15-C WT	GCGGCGAGACGATAGGT
inhA 2	inhA: -15-T	CGCGGCGAGATGATAGG
embB 1	embB 306 WT	ACATCCTGGGCATGGCC
embB 2	embB 306 ATA	TACATCCTGGGCATAGCC
embB 3	embB 306 GTG	ATCCTGGGCGTGGCC

Fig. 1 Sequences of oligonucleotide probes used in DNA-biochip assay. 'WT' indicates wild type probe (other probes are mutant). Codons or bases mutated are indicated in bold.

Fig.1.jpg

Pattern of immobilization				
rpoB 1	rpoB 2	rpoB 3	rpoB 4	InhA 1
rpoB 1	rpoB 2	rpoB 3	rpoB 4	InhA 1
embB 1	rpoB 5	rpoB 6	rpoB 7	rpoB 8
embB 1	rpoB 5	rpoB 6	rpoB 7	rpoB 8
rpoB 9	rpoB 10	inhA 2	embB 2	embB 3
rpoB 9	rpoB 10	inhA 2	embB 2	embB 3

Fig 2: Pattern of probe immobilization on DNA-biochip.

Fig.2.jpg

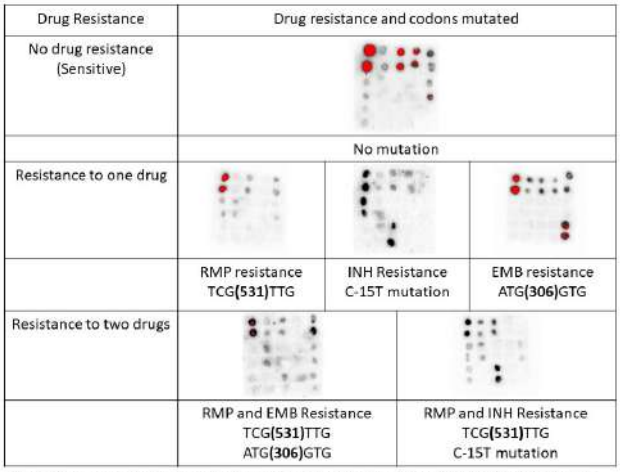

Fig 3: Representative images obtained after hybridization of amplified DNA with biochip.

Fig.3.jpg

Contribution of Common and Rare Genetic Variants in CEP72 on Vincristine-Induced Peripheral Neuropathy in Brain Tumor Patients

Friday, 9th April - 14:00: Flash Session 1 (Main Room) - Poster - Abstract ID: 68

Mrs. Marije Klumpers [1], Mrs. Annouk Brand [2], Ms. Marina Hakobjan [2], Dr. Giovanna Gattuso [3], Dr. Elisabetta Schiavello [3], Dr. Monica Terenziani [3], Prof. Maura Massimino [3], Dr. Corrie Gidding [4], Prof. Henk Jan Guchelaar [5], Dr. Maroeska te Loo [6], Dr. Marieke Coenen [7]

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Purpose: Peripheral neuropathy is a common side effect of vincristine. Studies implicated a role for a genetic variant in *CEP72* in vincristine-induced peripheral neuropathy. This study aims to evaluate this association in a cohort of brain tumors patients, to perform a cross-disease meta-analysis and explore the protein-coding region of *CEP72*.

Experimental Design: 104 vincristine-treated brain tumor patients were genotyped for *CEP72* rs924607, and sequenced for the protein-coding region. Data regarding patient and treatment characteristics, and peripheral neuropathy, were collected. Logistic regression was performed for rs924607 replication (including a meta-analysis) and analyses of other common variants. A weighted burden analysis was applied to evaluate impact of overall genetic variation in *CEP72*.

Results: Analysis of 24 cases and 80 controls did not show a significant association between *CEP72* rs924607 and vincristine-induced peripheral neuropathy (OR (95% CI) 2.076 (0.359 – 11.989), p=0.414). When combined with eight cohorts (1,098 cancer patients), a significant increase in risk for neuropathy was found for patients with a TT genotype (OR (95% CI) 2.22 (1.37 – 3.61), p=0.001). Additionally, a missense variant (rs12522955) was significantly associated (OR (95% CI) 2.3 (1.2 – 4.4), p=0.041) and patients with severe neuropathy carried more impactful genetic variants in *CEP72* coding regions (p=0.039).

Conclusions: This study could not confirm the association of *CEP72* rs924607 in vincristine-induced neuropathy in a cohort of brain tumor patients, but did contribute to its suggested effect when combined with other cohorts. In addition, the importance of other genetic variations in *CEP72* on vincristine-induced peripheral neuropathy was demonstrated.

Combined geno- and phenotyping in DPD diagnostics is of added value in patients with a DPYD variant and decreased DPD enzyme activity

Friday, 9th April - 14:00: Flash Session 1 (Main Room) - Poster - Abstract ID: 71

Dr. Bianca van den Bosch [1], ***Dr. Charolotte Ockeloen*** [2], ***Mr. Aron Raaijmakers*** [3], ***Mrs. Manon Hijmans-van der Vegt*** [4], ***Dr. Jörgen Bierau*** [1], ***Mrs. Judith de Vos-Geelen*** [5], ***Dr. Annelieke Willemsen*** [6], ***Dr. Marieke Coenen*** [7]

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Introduction: Dihydropyrimidine dehydrogenase (DPD) enzyme deficiency is associated with severe fluoropyrimidine-associated toxicity. Four clinically relevant variants in the *DPYD* gene are associated with a DPD enzyme deficiency.*DPYD* genotyping is widely used prior to fluoropyrimidine treatment to improve patient safety. However, only 25% of patients who carry a variant show a decreased DPD enzyme deficiency in peripheral blood mononuclear cells (PBMCs). The aim of our study was to investigate if DPD phenotyping using an *ex vivo*PBMC assay has added value when combined with *DPYD* genotyping in predicting fluoropyrimidine-related toxicity. **Methods:**228 patients from one hospital were included in this retrospective cohort study. Patients were genotyped for four *DPYD* variants associated with a decreased DPD activity. The individual starting dose was based on individual geno- and phenotype results. **Results:** The percentage of patients who developed severe toxicity (Common Terminology Criteria for Adverse Effects grade 3 or higher) in the variant carrier group (*DPYD*v) is similar to a previous prospective trial (32% resp. 39%). In the decreased DPD enzyme activity group (DPD^{low}) 27% developed severe toxicity, comparable to the control group of patients without a variant and normal DPD enzyme activity ($DPYD^{n}$-DPD^{n}; 29%). The mean dose intensity in the *DPYD* group and DPD^{low} group was lower than in the $DPYD^{n}$-DPD^{n} group (78% and 84%, resp. vs. 91%). Furthermore, the majority of the $DPYD^{v}$ and DPD^{low} patients received an initial dose reduction (63% and 46% vs. 19% in the $DPYD^{n}$-DPD^{n} group). The patients with a variant and decreased DPD enzyme activity ($DPYD^{v}$-DPD^{low}) experienced more severe toxicity than the $DPYD^{n}$-DPD^{n} group (50% vs 29%), even though this group received the lowest initial dose and whole treatment dose intensity on average. These patients also seem to have more severe toxicity than patients in other groups, as 33% experienced grade 4 toxicity and one patient died (grade 5 toxicity). **Discussion:** Group sizes are too small to show statistically significant differences, but our findings indicate that using a combined genotype-phenotype approach could be useful to identify patients with an increased risk of severe toxicities (e.g. the $DPYD^{v}$-DPD^{low} group). A prospective study in a larger cohort is required to provide statistical substantiation and to investigate which starting dose alterations should be considered in the*DPYD* variant patients with a decreased DPD enzyme activity and patients with only decreased DPD enzyme activity (in whom none of the four tested variants were present).

A targeted and combined nanosystem-mediated antitumor strategy to HCC

Friday, 9th April - 14:00: Flash Session 1 (Main Room) - Poster - Abstract ID: 77

Ms. Dina Farinha [1], ***Dr. Michael Migawa*** [2], ***Dr. Ana Bela Sarmento*** [3], ***Dr. Henrique Faneca*** [3]

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Introduction: Hepatocellular carcinoma (HCC) represents about 75–85% of primary liver cancers and is the fourth most common cause of cancer-related death worldwide. Sorafenib is a protein kinase inhibitor with activity against many protein kinases.However, the long exposure of cells to sorafenib promotes chemoresistance. This cell resistance can be minimized by combining sorafenib with selumetinib an inhibitor of mitogen-activated protein kinase (MEK). However, both sorafenib and selumetinib have an inherent toxicity that leads to highly undesirable side effects. In order to overcome these problems, we have developed a new biodegradable and biocompatible hybrid nanosystem, composed of a polymeric core coated by a lipid bilayer containing the targeting ligand GalNAc,with the ability to simultaneously and specifically deliver both drugs into HCC cells.
Methods: The physicochemical characterization of hybrid nanosystems (HNP) and their components was performed by dynamic light scattering, zeta potential, transmission electron microscopy and matrix-assisted laser desorption ionization - time of flight mass spectroscopy. Cellular binding, specificity of HNP and uptake were evaluated through flow cytometry and confocal microscopy. The therapeutic activity was evaluated namely through: cell viability by the Alamar Blue assay; cell death and mitochondrial membrane potencial by flow cytometry; caspases activity by luminescence; and molecular targets levels by Western blot.
Results/Discussion: Our results show that these new hybrid nanosystems present high stability and loading capacity, suitable physicochemical properties, and high specificity for HCC cells. Moreover, our datademonstrate that the hybrid nanosystems containing both drugs significantly enhance cell death in HCC cell lines, but not in non-tumor cells, when compared to the same amount of free drugs. This potentiation of the antitumor effect mediated by the new hybrid nanosistems was shown to be carried out by increasing programmed cell death. In fact, we observed not only a strong reduction in the mitochondrial membrane potential, but a significant increase in the activity of caspases 3/7 and caspase 9, as well as a greater number of positive cells for annexin-V, all characteristic indicators of the apoptotic process. A synergistic antitumor effect of the two drugs when encapsulated in the new hybrid nanosystems was verified not only in 2D cell cultures but also in 3D ones, where it was observed an almost total death of the tumor mass with drugs loaded in nanosystems. This study demonstrates that this new drug formulation presents translational potentialto improve the therapeutic approaches against HCC.

Acknowledgements

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Chemical design of lipophilic uncouplers of oxidative phosphorylation for treatment of non-alcoholic fatty liver disease and type 2 diabetes

Friday, 9th April - 14:00: Flash Session 1 (Main Room) - Poster - Abstract ID: 86

Ms. Daria Vedeniapina [1], ***Ms. Kseniya Vlasova*** [2], ***Mr. Maxim Abakumov*** [3], ***Mr. Petr Ostroverkhov*** [1], ***Mr. Stepan Vodopianov*** [4]

1. *"MIREA-Russian Technological University" RTU MIREA,* ***2.*** *Moscow State University(MSU) named after M.V. Lomonosov, Pirogov Russian National Research Medical University,* ***3.*** *Pirogov Russian National Research Medical University, National University of Science and Technology (MISIS),* ***4.*** *Moscow State University(MSU) named after M.V. Lomonosov, National University of Science and Technology (MISIS)*

Introduction. The project is devoted to developing an effective dosage form of lipophilic 2,4-dinitrophenol derivatives for delivery to the liver as a promising treatment of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (type 2 diabetes). The resulting system loaded with the synthesized 2,4-dinitrophenol derivative should be delivered to liver cells, where it will act as a proton ionophore, transferring protons into the mitochondrial matrix with the release of heat. Such process leads to accelerated fat oxidation. Nowadays few researchers have addressed the issue of 2,4-DNP and its oral administration formulations as a type 2 diabetes treatment. However, in the case of oral dosage forms, it is rather difficult to carry out controlled delivery and release of the drug in the target organ. This project involves the synthesis of lipophilic derivatives of 2,4-dinitrophenol and their incorporation into liposomes for controlled release for intravenous administration.

Purpose of the study. Development and optimization of methods for the synthesis of a number of 2,4-dinitrophenol derivatives, such as 2,4-dinitrophenol esters with different chain lengths of the substituent, loading them into liposomes and test *in vitro* using ATP luciferin-luciferase assay.

Materials and methods. 2,4-dinitrophenol, palmitic acid, hexanoic acid, propionic acid, luciferin, 4T1 luciferase cells, eggPC, DSPC.

Results. Lipophilic derivatives of 2,4-dinitrophenol with different chain lengths of the substituent have been obtained and successfully isolated. Using ATP luciferin-luciferase assay was shown efficacy of each derivative in comparison to free 2,4-DNP. Derivatives was incorporated in liposomes consisting of eggPC or DSPC with different melting point. The loading of the esters was 3-5 times higher (depending on the chain lengths of the substituent) than free 2,4-DNP. The *in vitro* test of the liposomal formulations showed prolonged inhibiting ATP synthesis due to sustained release of active molecules. The effect was depended on lipid composition and membrane state.

Findings. The obtained compounds were shown to be active in inhibiting ATP synthesis and were loaded into liposomes. Also, the optimal lipid composition was shown to produce stable and highly effective formulation for treatment of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus.

This work was supported by a grant from the Russian Science Foundation No. 20-73-00333.

Technical Theory of Refuting the use of Amylase Concentration Index in Clinical Tests for diagnostic & Monitor Treatment of Obesity

Friday, 9th April - 14:00: Flash Session 1 (Main Room) - Poster - Abstract ID: 81

Dr. Gihan Gawish [1]

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Introduction: Although obesity relates to demographic and heritable characteristics, a large proportion of the heritability of obesity remains unexplained. Recent studies observed that KSA is now among the nations with the highest obesity and overweight prevalence rates. We have suggested that the theory of this problem is based on the failing of protocol establishment for each personalized treatment, due to the low number of laboratory tests related to genetic defects of biomarkers that have functions in metabolism of nutrients which may have a major role of personalized obesity in SA. Recently, the efforts of some doctors in Saudi private hospitals have included the examination of amylase enzyme concentration within the diagnostic tests for obesity as a metabolic enzyme.Based on genetics we have suggested that there is a wide difference between the concentrations of enzymes and their activities.

Objectives:Our aim was to establish a screening scheme of biochemical and genetic markers relate to obesity. Our first aim to approach our vision was to study the relationship between the activity of salivary amylase and BMI, to compare between activities and concentrations of amylase specimens.It also aimed to identify the CNV of amylase gene (AMY1) and its relation to BMI.

Methods:Four hundred specimens from adults obesity with 30 to35 BMI participated in this study that was chosen randomly from those who were free from chronic diseases like blood pressure, diabetics and endocrine diseases. Saudis with normal weight volunteered to donate control specimens with 18.5 to24 BMI. The biomarkers were estimated by taking three specimens from each person, they were collected for measuring the activity of amylase 1 by using Amylase Assay Kit and oral mucosa for characterize CNV using qPCR.

Results showed that the effect of heredity on obesity was significant relationship between the body mass index and the prevalence of one parent with obesity ($P \leq 0.04$). On the other hand there were no significant between the numbers of primates used for measuring AMY1-CNV between normal weight and obese people for TGMS, PRT12A and PRT1H microsatellite genes while the results showed highly significant difference ($p \leq 0.004$) between the activity of amylase and obese. The most approached aim of this study that it showed no significant between amylase concentrations and BMI. Also,it confirmed that no significant between enzyme concentrations and enzyme activities of amylase.

Conclusions:We have recommended the physicians to avoid and to stop request the test of amylase concentration for diagnostic obesity as it may be wasted chemicals, time and patients budgets. Also,We have highly recommended the obese patients to consider the requests of amylase concentration test as a monitor of obesity from doctors because that is may be a precursor of using a medicine affect the pancreatic functions and may lead to acute pancreatitis.

Integration of polygenic risk into an ancestry aware absolute model for breast cancer

Friday, 9th April - 14:00: Flash Session 1 (Main Room) - Poster - Abstract ID: 70

Dr. George Busby [1], ***Mr. Saurabh Hebbalkar*** [1], ***Mr. Paul Craig*** [1], ***Mr. Paolo Di Domenico*** [1], ***Dr. Giordano Botta*** [1]

1. *Allelica Srl*

Introduction

A woman's risk of developing breast cancer (BC) is linked to both genetic and non-genetic factors. From a genetic perspective, BC has a complex etiology that depends on the combination of rare mutations with high penetrance, such as the *BRCA1* and *BRCA2* genes, intermediate-risk variants in genes such as *PALB2*, *CHEK2* and *ATM*, and multiple common BC susceptibility loci that have been discovered through GWAS. Prediction of BC risk attributable to genetics can be inferred from Polygenic Risk Scores (PRS) which have be used to identify, for example, women who approach the BC risk of an average 50 year old, up to 15 years earlier than expected. A large driver in the progress of PRS for BC has been the availability of genomic and matched phenotyped data in large prospective cohort studies such as the UK Biobank (UKB). Given that such projects require national coordination ,they contain populations representative of the ancestry of particular countries, and are therefore by design not representative of global ancestry. This poses a challenge for researchers developing PRS on such datasets who wish to transfer them to populations with different ancestries.

The aim of this study is to assess the transferability of PRS developed on European populations to individuals with non-European ancestry.

Methods

We first developed a new PRS for BC using summary statistics from a GWAS for BC and applied 5 different PRS algorithms on independent Validation and Testing datasets from a total of 11,496 Breast Cancer and 151,186 controls from the UK Biobank. We ran the best performing PRS on 4 ancestry subsets of the UK Biobank and assessed its ability to discriminate cases and controls.

Results

The best performing PRS utilised a Stacked Clumping and Thresholding approach which had greater predictive power than published scores (AUC=0.677 (0.667-0.686)). We applied this PRS to sub-continental ancestry groups from UKB and calculated validation statistics (Table). We then implemented a Cox proportional hazards survival model to identify the probability of Breast Cancer by age 75, using ancestry specific data from the UKB (Figure).

Discussion

Our analysis shows that a BC PRS developed in European populations can be transferred to different ancestries, but the proportion of individuals at increased risk is smaller. Whilst the BC PRS identifies 8% of individuals at a greater than three times the population risk of disease, this drops to 3% for South Asian, 4% for East Asian and 2% for African ancestry groups. Whilst more data from diverse populations will greatly add to the validity of PRS in non-European ancestry populations, our approach suggests that some benefit can nevertheless be gained from European PRS in these groups.

Table 1: A new BC PRS predicts risk in ancestry subsets of the UKB. AUC = Area under the Curve; OR = Odds Ratio per standard deviation of PRS; 3X, 4X, 5X = proportion of the populations at 3,4 or 5 fold increase in risk compared to the remainder based on analysis of UK prevalence data

	European	South Asian	East Asian	African
#Controls	151,186	3,376	893	4,202
#Cases	11,496	176	45	161
AUC	0.68 (0.67-0.69)	0.60 (0.54-0.64)	0.64 (0.54-0.72)	0.56 (0.49-0.62)
OR	1.74 (1.70 - 1.78)	1.22 (1.01 - 1.49)	1.51 (1.03 - 2.22)	1.23 (1.00 - 1.52)
3x	92	97	96	98
4x	98	99.5	99.5	99.5
5x>	99.5	#	#	#

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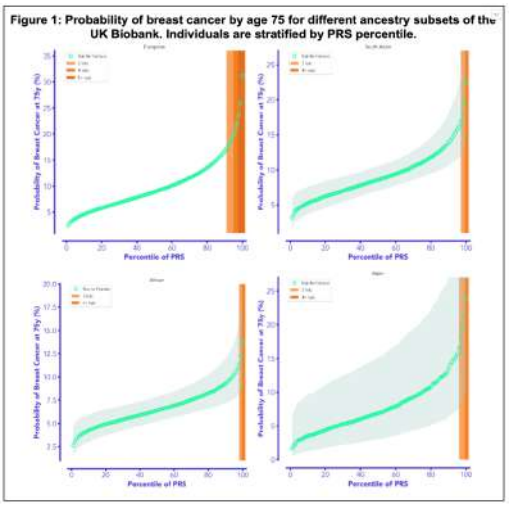

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Pharmacogenetic drug use and hospital re-admissions among older inpatients with depression: a cohort study in Central Denmark Region between 2014 and 2018

Friday, 9th April - 14:00: Flash Session 1 (Main Room) - Poster - Abstract ID: 85

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Introduction: Older adults (aged 65+ years) often suffer from depression and the use of pharmacological treatment including pharmacogenetics (PGx) drugs is widespread. Still, little is known about the impact of PGx in older adults with depression.

We aimed to evaluate the potential of PGx in older adults (>65 years) with depression, by identifying the frequency of PGx psychotropic drug users and estimating whether PGx psychotropic drug use is associated with the lengths of first psychiatric hospital admission and the risk of re-admission.

Methods: For this retrospective cohort study we included older adults with a depression diagnosis (ICD-10: F32-33) admitted at a psychiatric department in Central Denmark Region between 2014-31/12/2018, covering approximately 25% of the Danish population. Data were collected via Business Intelligence at Central Denmark Region as part of a quality assurance project. Data included information on drug administrations during hospital admissions. Exposure to PGx psychotropic drugs was defined as having received an administration for at least one of the 21 actionable PGx psychotropic drugs, used in Denmark, anytime during an admission.

In a subgroup analysis we followed patients from the first day of their first-time hospital admission (index hospitalization) due to depression between 2015-31/12/2017, until first readmission within 1- year after discharge, emigration, death or end of study period. We assessed the association between PGx drug use during the index hospitalization and length of index hospitalization using linear regression analysis and present the β estimate with p-value ($p < 0.05$ = statistically significant) and means with standard error (SE). We used a logistic regression analysis to assess the association between PGx drug use during the index hospitalization and one-year risk of first re-admission and reported odds ratios (OR) with 95% confidence intervals (CI). We adjusted for sex, age, psychiatric hospital departments, diagnosis when drug was administered, previous psychiatric diagnosis or psychiatric hospital contacts, calendar year of depression diagnosis and non-PGx potentially drug-drug interacted psychotropic drugs use.

Results: Among 726 older inpatients with depression, 81.2% of 65-79 and 69.6% of >80 years old used at least one PGx psychotropic drug. The most common used PGx psychotropic drugs were sertraline, venlafaxine, citalopram and nortriptyline, related to the enzymes CYP2C19 and CYP2D6. Among the subgroup of 381 patients, usage of at least one PGx psychotropic drug was associated with a longer first psychiatric hospital admission (days) ($\beta = 10.36$; SD 2.98, $p < 0.001$) and about a three times higher risk of readmission (OR = 3.07; 95% CI: 1.59-6.46).

Conclusion: The implementation of PGx has potential to improve the quality of pharmacological treatment in older inpatients with depression. Especially CYP2C19 and CYP2D6 gene variants should be identified before the initiation of psychotropic drug treatment.

Identification of basic microRNA markers of follicular and papillary thyroid tumors

Friday, 9th April - 14:30: Flash Session (Main Room) - Poster - Abstract ID: 54

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MicroRNA (miRNA) are pivotal regulators of gene expression in eukaryotic cells including genes implicated in pathological processes such as development of follicular and papillary thyroid cancers (TC).The quantitative assessment of miRNA levels in malignant thyroid tissues adds significant information facilitating recognition of the cancer subtype and elucidating tumor growth dynamics; it is also helpful in assessing drug resistance of certain tumor subtypes One major problem are the high false discovery rates (FDR, as a rule they exceed 1 x 10^{-6}), if one uses only a single marker, and this holds true for all known miRNA biomarkers. It means that in the context of malignant transformation the prognostic value of miRNA biomarkers is high enough only in case of simultaneous analysis of a large number of such biomarkers in tissue samples from the same patient or if the number of patients is large enough. This is why miRNA biomarkers are only seldom used for diagnosis and prediction of prognosis of TCs.

The aim of this study was to conduct a total screening of miRNAs that are abnormally expressed in case of follicular and papillary thyroid cancers and identification of the markers of malignant transformation that are associated with minimal FDR.

We have explored the samples of TC tissues from 50 patients including 30 samples of follicular thyroid cancer tissues and 20 samples of papillary thyroid cancer tissues and also 9 samples of tissues of healthy subjects. Each sample was accompanied by a histological description and anonymous case history.

Based on the results of deep sequencing, markers were selected for each subtype of thyroid cancer, which have the lowest false detection rate (FDR) when compared with normal tissues, that is, the most promising from the point of view of application in the field of diagnosis and prognostics of thyroid cancer.

For follicular cancer (adenoma and carcinoma), these markers were miR-151b, miR-96, miR-182, miR-183, miR-517a, miR-518b, miR-1247, miR-150, miR-1249. For papillary thyroid cancer (adenoma and carcinoma): miR-3687, miR-21, miR-31, miR-222, miR-221, miR-146b, miR-181b, miR-451a, miR-486, miR-1179. According to our data, changes in the expression level of miR-192 and let-7a were found only in patients with recurrent thyroid cancer and, most likely, can be used as a prognostic factor.

This work was supported by the scholarships of the President of the Russian Federation for young scientists and graduate students (SP-1457.2019.4).

Feasibility of Panel of Pharmacogenetic markers Associated with Adverse Drug Reactions in Fluoropyrimidine and Irinotecan-treated cancer patients enrolled in the PREPARE study- Results from a preliminary analysis

Friday, 9th April - 14:30: Flash Session (Main Room) - Poster - Abstract ID: 60

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Introduction: Ubiquitous Pharmacogenomics (U-PGx) consortium was set up in 2016 under the leadership of Leiden University Medical Center with the aim of bringing pharmacogenetic into the clinical practice in Europe (www.upgx.eu). With the financial support of the European Community Horizon2020, a multicentric prospective clinical trial (PREemptive Pharmacogenomic testing for prevention of Adverse drug Reactions, PREPARE) was initiated in 7 European countries including Italy. PREPARE is a prospective, controlled, block□randomized clinical study with the aim of assessing the clinical utility of implementing a panel of PGx markers into routine care (VanDerWouden, et al. ClinPharmTher, 2017). CRO-Aviano Cancer Center in Italy enrolled oncological patients treated with FPs/IRI treatment. The aim of this preliminary analysis was to evaluate, on this homogeneous subgroup of patients, the feasibility of implementing a panel of pharmacogenetic markers.

Methods: The 37-months enrollment period was split into two (Standard of care or PGx testing) time-blocks and ended in July 2020. Enrolled patients were genotyped within a 4-days turnaround time using with an allelic discrimination-based method (SNPline platform). In the standard of care arm, patients and clinicians were blinded for their PGx results. In the PGx testing arm, patients' PGx results were incorporated in the (electronic) medical records along with clinical data and combined with a clinical decision support system. Physicians chose whether to use these results to guide drug and dose selection. All patients were followed for 3 to 18 months.

Results: In total, 1,232 patients were recruited from March 2017 to July 2020; 622 in the pharmacogenomic testing arm, and 610 in the standard of care arm. A preliminary analysis performed in both the control and study arm, pointed out that only 4,3% of the genotyped patients carried no actionable variants, while 95% carried at least one actionable variant. In both arms 50% of patients received a FPs-based therapy and 10% Irinotecan and colorectal cancer was the most represented disease overall. The distribution of patients' with *DPYD*and *UGT1A1* actionable genotype was similar in both arms: 12.7% and 13.2% of patients were homozygous *UGT1A1*28* variant allele carriers in Standard of care arm and Pharmacogenomic testing arm, respectively; while 3.4% and 4.8% carried at least one of the four actionable *DPYD*variants.

Discussion: From a preliminary analysis on FPs/IRI treated patients enrolled in the PREPARE study it could be hypothesized that implementing PGx-guided drug and dose selection may be a feasible approach in the clinical setting of CRO-Aviano hospital in 4-days turnaround time. A huge international effort will hopefully demonstrate whether a pre-treatment PGx approach will positively impact health outcomes, decision making and costs in several fields of pharmacology, including cancer.

Mammalian sperm DNA condensation differ among different species, a key to improve sperm DNA fragmentation analysis

Friday, 9th April - 14:30: Flash Session (Main Room) - Poster - Abstract ID: 61

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Introduction: Sperm cells present a highly particular DNA condensation that is acquired during sperm differentiation, where most part of histones are replaced by protamines. Protamines are key elements for DNA condensation and, while protamine 1 is more conserved among species, protamine 2 had evolved differentially, existing only a few species that retained its mature protein in its sperm DNA. Changes in protamine expression rates have been described to be associated to head sperm size and shape and, in those species that protamine 2 is present, a reduction of its expression is related to male infertility. DNA decondensation is used for different methods, as halo assay or Comet assay, to measure sperm DNA fragmentation which, in turn, is related to higher rates of male infertility and human miscarriage.

The present study aims to analyze the DNA decondensation capacity of sperm cells from different animals, including humans, in order to define the differential resistance of its nucleus, fact that might have implications in sperm DNA integrity diagnosis.

Methods: Species included in the study were Human, Equine, Donkey, Porcine and Bovine. Cryopreserved sperm samples were treated with lysis solutions to induce DNA decondensation and formation of sperm haloes. DNA decondensation included three lysis steps: first, a SDS+DTT incubation for 30 minutes; second, a DTT+NaCl treatment for 30 minutes; and third, a DTT+NaCl+Proteinase K treatment with a variable time of 0, 30 or 180 minutes. In these treatments, the effect in DNA decondensation of different incubation times in proteinase K in the lysis solution was tested by analyzing core diameter, halo diameter and the Halo/core ratio in at least 50 sperm per sample.

Results and discussion: The halo/core diameter, used as a representation of the degree of DNA decondensation, for 0 minutes, 30 minutes and 180 minutes of proteinase K incubation are depicted in Table I. Differences of halo/core ratio in different times were only observed in porcine and bovine sperm, where increasing degrees of DNA decondensation were found ($p<0.05$). Therefore, these results show that longer incubations with proteinase K lead to a higher DNA decondensation only in porcine and bovine, and did not induce a higher decondensation in human, equine and donkey. This evidence, coupled to the fact that porcine and bovine sperm present null or very low protamine 2 content, suggests that its presence might confer a higher DNA decondensation susceptibility.

Sperm DNA might have different degrees of DNA condensation, which can be associated to a higher difficulty of DNA decondensation, thus having implications in the sensitivity tests that assess sperm DNA integrity.

Table 1. Effect of Proteinase K decondensation in halo and core diameter in different species

	Proteinase K treatment (min)	Human	Equine	Donkey	Porcine	Bovine
Core with (mm)	0	7,11 ± 0,95	5,67 ± 0,55	5,83 ± 0,35	4,98 ± 0,50	4,34 ± 0,79
	30	6,62 ± 1,17	6,92 ± 0,58 [a]	6,32 ± 0,64	5,28 ± 0,30	6,05 ± 0,58 [a]
	180	8,19 ± 0,98 [b]	6,96 ± 1,60 [a]	7,15 ± 0,79 [a]	6,37 ± 0,61 [a,b]	7,16 ± 1,01 [a,b]
Halo + core diameter (mm)	0	32,45 ± 0,85	22,91 ± 1,46	25,18 ± 3,67	8,62 ± 1,04	10,36 ± 3,71
	30	27,74 ± 2,54 [a]	30,28 ± 1,30 [a]	24,55 ± 2,78	15,87 ± 1,32 [a]	20,15 ± 3,22 [a]
	180	37,76 ± 1,46 [a,b]	30,69 ± 2,41 [a]	29,32 ± 2,82 [b]	25,81 ± 1,53 [a,b]	29,17 ± 2,50 [a,b]
Halo / Core relation	0	4,68 ± 0,51	4,15 ± 0,47	4,40 ± 0,64	1,77 ± 0,20	2,40 ± 0,40
	30	4,32 ± 0,51	4,57 ± 0,53	4,00 ± 0,37	3,05 ± 0,14 [a]	3,36 ± 0,22 [a]
	180	4,77 ± 0,64	4,68 ± 0,63	4,17 ± 0,19	4,13 ± 0,39 [a,b]	4,19 ± 0,38 [a,b]

[a] Statistical differences compared to 0 min proteinase K ($p<0.05$)
[b] Statistical differences compared to 30 min proteinase K treatment ($p<0.05$)

Table.jpg

The membrane transporter OAT7 (SLC22A9) is not a susceptibility factor for osteoporosis in Europeans

Friday, 9th April - 14:30: Flash Session (Main Room) - Poster - Abstract ID: 65

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Introduction: The formation and maintenance of bone involves osteoclast-mediated bone resorption, osteoblast-mediated bone formation and remineralization. Sex steroid hormones, including their conjugated forms, contribute majorly to maintaining the well-balanced process of bone formation and maintenance. The elderly have an increased risk for osteoporosis due to accelerated bone loss and compromised bone strength. Osteoporosis affects hundreds of million people worldwide with major clinical consequences such as fractures, disabilities and mortality. Hence, it is important to discover markers for the identification of individuals at risk for developing osteoporosis. A multitude of genetic variants have been associated with low bone mineral density or increased fracture risk. Variants in the *SLC22A9* gene had been associated with osteoporosis in Korean females (Ahn et al., 2015, Korean J Physiol Pharmacol 19:319). We had recently shown that *SLC22A9*, encoding organic anion transporter 7 (OAT7), is an uptake transporter of estrone sulfate and identified several genetic variants in Europeans leading to functional consequences in vitro (Emami Riedmaier et al., 2016, Pharmacogenomics J 16:341). We therefore hypothesized that *SLC22A9* genetic variants may contribute to the pathophysiology of osteoporosis in Europeans.

Methods: To test this hypothesis, we examined the associations of *SLC22A9* variants with bone quality, fractures and serum bone turnover markers. We genotyped *SLC22A9* variants in 5701 (2930 female) subjects (age range 20-93 years) extracted from the cross-sectional population-based Study of Health in Pomerania (SHIP and SHIP-TREND) (Schürer et al., 2015, Dtsch Ärztebl Int. 112:365) covered by the Illumina Infinium HumanExome BeadChip version v1.0 (Exome Chip). Descriptive data (e.g. history of fractures), ultrasonography of the calcaneus as well as serum concentrations of carboxy-terminal telopeptide of type I collagen (β-CTX), amino-terminal propeptide of type I procollagen (PINP) and vitamin D were determined.

Results: A total of 23 missense variants in the *SLC22A9* gene were genotyped and 14 variants were detected. The 2 variants rs61742518 (p.T433M) and rs146027075 (p.I479M) occurred with minor allele frequencies of 2.68% and 0.96%, respectively, and were thereby the only low-frequency variants. The remaining 12 variants occurred only heterozygously and were rare variants with minor allele frequencies between 0.1% and 0.01% (5 variants) or occurring in single individuals (7 “singleton” variants). Comprehensive single variant statistical analyses revealed no association between low-frequency and rare *SLC22A9* variants and bone quality, fractures and bone turnover markers. The singleton variants rs200498139 and rs3737458 were significantly associated with β-CTX and PINP, respectively, after correcting for multiple testing. The two heterozygous individuals carrying either variant had very low β-CTX or PINP serum levels.

Discussion: Our results indicate that single genetic *SLC22A9* variants do not have a major impact on osteoporosis risk prediction in Europeans, yet findings need to be replicated in larger-scale studies.

Update on companion diagnostic

Friday, 9th April - 14:30: Flash Session (Main Room) - Poster - Abstract ID: 67

Dr. Jan Trost Jorgensen [1]

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Introduction

With the development of trastuzumab (Herceptin, Roche/Genentech), a new era in oncology drug development began. Not only was it a scientific and medical achievement but it also paved the way for the drug-diagnostic codevelopment model, where a predictive biomarker assay is developed in parallel to the drug. In 1998, the Food and Drug Administration (FDA) simultaneously granted approval to trastuzumab and the HER2 immunohistochemical (IHC) assay, HercepTest (Dako/Agilent). The HercepTest became the first companion diagnostic (CDx) approved by the FDA, and over the past more than 20 years the number of drugs that have been developed and launched with a predictive biomarker assay have steadily increased [1].

Methods

Based on the FDA 'List of Cleared or Approved Companion Diagnostic Devices' a brief analysis of the current landscape of regulatory approved CDx assay was performed. The analysis focused on biomarkers, drugs, clinical indications, analytical platforms, regulatory paths and status.

Results

At the end of 2020, the total number of CDx assays approved by the FDA was 44 [1]. Figure 1 shows the CDx approvals by year since the first approvals in 1998. Nearly all these assays are linked to hematological and oncological drugs.

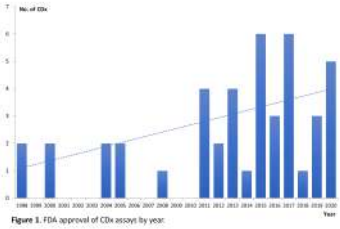
Looking at the analytical platforms for the different CDx assays, IHC and in situ hybridization (ISH) were the dominating technologies until 2011 when the first CDx based on the polymerase chain reaction (PCR) method was approved. As it appears from Figure 2, a total of 16 PCR based assays have been approved by the FDA, which makes it the most frequently used CDx platform. Within the last five years, next generation sequencing (NGS) has also made its way as a CDx platform and by the of 2020 the number of FDA approved assays was 6.

Most CDx assays are high-risk devices and classified as Class III, which requires a high level of regulatory control and submission of a Premarket Application (PMA). This has also been the situation for more than 80% of all the FDA approved CDx assays [1].

Conclusion

Predictive biomarker is an important element in the realization of precision medicine but looking at the number of CDx approved by the FDA over the last 20 years, it is relatively modest. However, within the past 8-10 years, the number of CDx assays has increased substantially. It is important to remember that without an accurate and reliable CDx assay, most targeted anti-cancer drugs lose their value. CDx assays are high-risk devices that requires a substantial documentation for assay quality and the clinical predictive properties, which might be one of the reasons for the relatively low number of FDA approvals.

- FDA. List of Cleared or Approved Companion Diagnostic Devices. Update: 11/16/2020.



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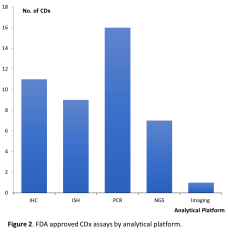

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A non-invasive tool to quantify autonomic dysfunction, A prognostic indicator in COVID-19

Friday, 9th April - 14:30: Flash Session (Main Room) - Poster - Abstract ID: 83

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BACKGROUND: The Outbreak of SARS-CoV-2 has caused a major pandemic posing a threat to the millions of lives all over the world. The evidence show that there is a relation between the autonomic nervous system and coronaviruses and likewise, levels of inflammatory markers - C-reactive protein (CRP) and autonomic dysfunction. Autonomic dysfunction is elicited using heart rate variability which in turn quantified using autonomous regulatory index (ARI). Hence this study was conducted to determine if ARI measured using patented NEUROCOR Precision HRV® Solution instrument could be used as a non-invasive measure of autonomic dysfunction among COVID-19 subjects.

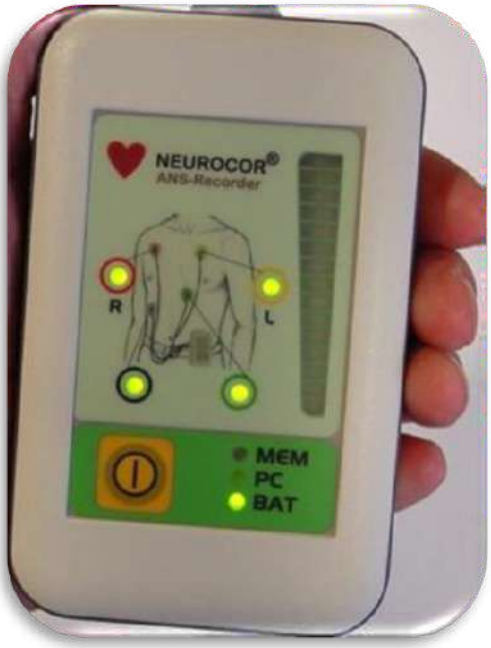
MATERIALS & METHODS: An exploratory study was conducted among randomly selected 22 COVID-19 male patients aged more than 18 years, admitted to COVID ward, Victoria Hospital, Bengaluru for 5 days, using ANS Recorder, a non-invasive heart rate variability recorder heart rhythm data were collected, one test per day continuously for 5 days and a patented NEUROCOR Precision HRV® Solution, an ANS Analysis Software instrument was used to record, analyze and interpret the heart rate variability in terms of ARI and CRP levels were measured. Data was analyzed using SPSS version 18.0. A P value of < 0.05 was considered statistically significant

RESULTS: The occurrence of autonomic dysfunction in COVID-19 patients using the Patented NEUROCOR Precision HRV® Solution was found to be among 50.0%. The median scores of average ARI indices were significantly lesser among those with higher health risk (28.39) compared to those with lower health risk (65.95) (P<0.05). The Median ARI index showed a weak negative correlation (r = -0.13, P>0.05) with CRP (P>0.05). ARI index showed a significantly excellent predictive ability in detecting the higher health risk with the areas under the curves (AUC) being 0.93 with an optimal cut-off of 40.85 with maximum sensitivity and specificity of 100.0% and 93.0%.

DISCUSSION:

- The occurrence of autonomic dysfunction in COVID-19 patients using the Patented NEUROCOR Precision HRV® Solution was found to be among 50.0%. Autonomic regulatory index (ARI) index had a significantly excellent predictive ability in detecting the higher health risk in COVID-19 patients. The median scores of average ARI indices were significantly lesser among those with higher health risk compared to those with lower health risk.

The median ARI index showed a weak negative correlation with C-reactive protein levels (CRP) indicating lower the ARI indices, the higher will be the CRP levels but it was not statistically significant



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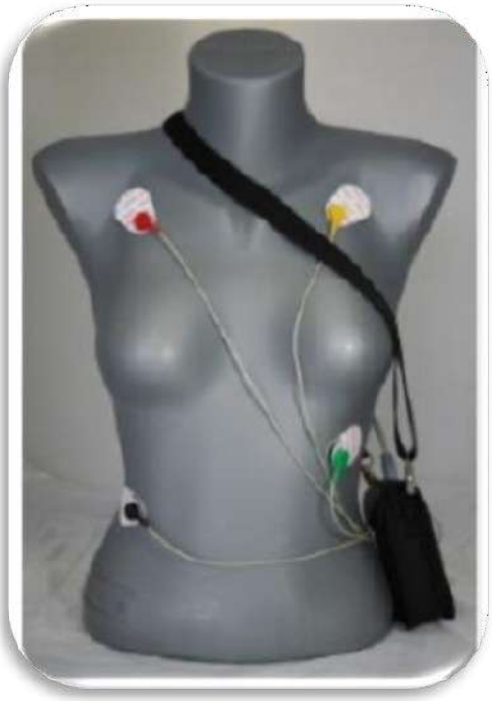

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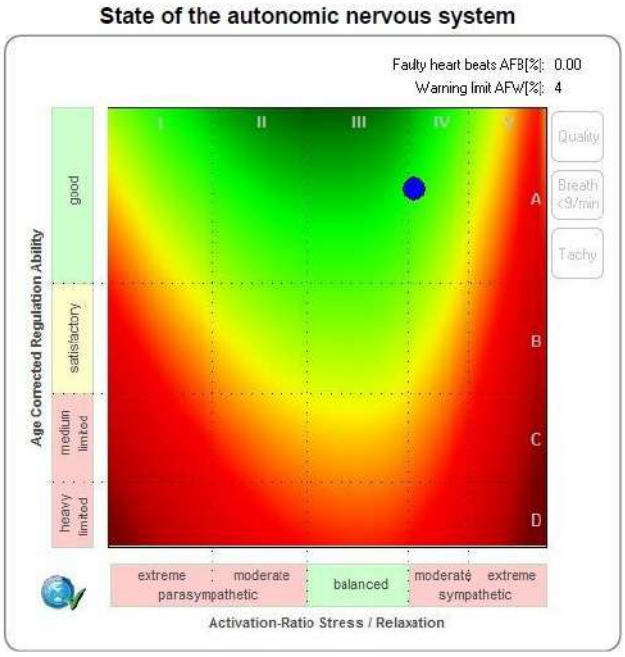

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