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Abstracts

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S01
High-Throughput Technologies in Personalized Medicine

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Genetic research and personalized medicine have significantly benefitted from the advent of high-throughput technologies. Providing the possibility to explore the whole genome at the same time and to potentially identify novel variants, these technologies allow carrying out hypothesis-free studies, therefore providing a powerful instrument to untangle the complexity of the human genome and the role of genetic modifications in diseases and response to pharmacological treatments. During the last decades, microarrays have rapidly evolved and the range of their applications has significantly expanded. Microarrays have been developed to genotype single nucleotide polymorphisms (SNP), to measure the expression of genes and non-coding RNAs as well as proteins. Next-generation sequencing has become the new gold standard for research and diagnosis in many fields, but despite its rapidly evolving precision and cost effectiveness, microarrays continue to provide a number of advantages and are therefore largely used in biology and medicine. In this talk I will provide an overview of the applications and advantages of different high-throughput technologies and discuss how their implementation is impacting on pharmacogenomics and speeding up the achievement of personalized medicine in different disorders.

S02
Cytogenomics in Cancer Pathology

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Genome instability shapes the genomic landscape of cancers and presents itself in many forms with variable clinical outcomes. It is thus pivotal to our understanding of cancer to be able to recognize the different (sub-)classes that result from genome instability. Next-generation sequencing (NGS) is the technique of choice to decipher the genomic landscape of cancers. The first challenge for the implementation of NGS in cancer research and diagnostics is to handle nucleic acids isolated from clinical specimens reliably and effectively. For diagnostics of solid malignancies, formalin fixation followed by paraffin embedding (FFPE) has been routine procedure for tissue preservation over the past 100 years. These FFPE archives now form an invaluable resource for biomarker discovery studies. Newly, liquid biopsies offer an alternative source for cancer research and diagnosis by NGS and frequently concentrate on circulating free nucleic acids isolated from peripheral blood. The second challenge for the implementation of NGS is not the wet-laboratory routine itself, but the increased dependence on data storage, transport and data-analysis infrastructure, as well as the expertise to interpret the data and include public data. At VUMC we have implemented NGS for routine diagnostics using FFPE material of chromosomal copy number aberrations and point mutations and are in the process to include translocations. Great progress has been made at VUMC in liquid biopsy analysis by NGS for blood-based pan-cancer, multiclass diagnostics. In this seminar, application of NGS in translational research will be illustrated with studies of lymphomas, colorectal cancers and low-grade gliomas.

S03
Cancer Treatment and Emphasis on Precision

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The field of pharmacogenomics is focused on the characterization of genetic factors contributing to the response of patients to pharmacological interventions. Drug response and toxicity are complex traits; therefore the effects are likely due to multiple genes. The investigation of the genetic basis of drug response has evolved from a focus on single genes to relevant pathways to the entire genome. The scope of this talk is to provide the current status of germline genomic studies in cancer patients treated with chemotherapy, the methods for discovery and implications for patient care. Large clinical trials enriched with genome-wide association studies (GWAS) provide an unprecedented opportunity for a comprehensive and unbiased assessment of the heritable factors associated with drug response. In oncology, germline genomics is still relatively unexplored, particularly in reference to biomarkers of patient survival. In this presentation, results from GWAS efforts in oncology and the use of somatic information from the cancer genome are presented, within the large context of achieving precision in treatment. Challenges and opportunities in translating heritable genomic discoveries to patients are also discussed.

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S04

Tumour Microenvironment and Response to Therapy

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Cancer cells develop resistance to chemotherapy and radiation by exploiting several biological responses, including DNA repair activity and apoptosis inhibition. A tumor is not, however, a cancer cell aggregation, but a tissue with defined morphology composed by cancer cells and stroma (fibroblast and vasculature), as well as a variety of infiltrating immunity-related cells. Survival of cancer cells within this neoplastic tissue under cytotoxic stress strongly depends upon the reaction of the noncancerous component. The density and functionality of the intratumoral vasculature largely varies among tumors and defines the accessibility of drugs and biological agents to cancer cells. Moreover, intratumoral oxygen availability may become severely compromised, so that vasculature-dependent hypoxia becomes the cause of upregulation of HIF- and Akt-dependent pathways, triggering anaerobic metabolism and resistance of cancer cells to apoptosis. As the ionizing radiation killing effect strongly depends upon oxygen concentration, radioresistance is inevitable in poorly vascularized tumors. Intratumoral acidity on the other hand, a result of anaerobic glucose usage, compromises the efficacy of many chemotherapy agents and increases cancer cell metastatic potential. Cross-talk between activated fibroblasts, vessels and cancer cells is probably a major pathway for the survival of 'functional tissue units' within the shrinking tumor mass that become the seed for a subsequent re-growth and tumor recurrence. The acidic and hypoxic intratumoral conditions is also an important suppressor of tumor immunity, so that cytotoxic lymphocytes fail to control tumor growth. Targeting stroma cell interaction with cancer cells is a promising field of research towards individualized anti-cancer strategies.

S05

Pharmacogenomics of Tyrosine Kinase Inhibitor Resistance

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Tyrosine kinase inhibitors (TKI) are small molecules, applied in the treatment of various malignancies such as leukemic diseases or solid tumors. Efficacy and risk of side effects, however, underly substantial inter individual variation. E.g. one of the first TKI, imatinib, was tremendous successful in treatment of chronic myeloid leukemia (CML) and it is still considered as first-line medication. Further developments were nilotinib or dasatinib. However, development of drug-resistance remains a major problem. Chemotherapy resistances may occur on certain levels. First, pharmacodynamic resistances e.g. against imatinib are caused by mutations in the BCR-Abl kinase domain or overexpression of the BCR-Abl fusion gene. In contrast, gain-of-funtion mutations in the EGF receptor functional domain are mandatory for efficient binding of gefitinib. Second, pharmacokinetically mediated resistances may be driven by overexpression or variances in efflux transporters, such as ABCB1 (P-glycoprotein, P-gp) or ABCG2 (BCRP). More recently, there has been an increasing understanding that side effects of TKI such as sunitinib are modulated by variants of the cytochrome P450 system or within cytokines. Of particular interest is the increasing knowledge on the deregulation of transporters through specific microRNAs that are differentially expressed in presence of TKI. The lecture will give a general overview about the field and some specific insights of experimental data.

S06

Clinical Implementation of Host Pharmacogenomics: Focus on Colorectal Cancer

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Colorectal cancer (CRC) represents one of the most common malignancies and causes of cancer-related deaths worldwide. Despite the introduction of new therapeutic agents and the great improvement achieved in the response rate and patient's survival, a remarkable interindividual variability in therapy outcome still represents a challenge in the management of CRC. Great research efforts have been focused on elucidating the contribution of the host genetic variability on the outcome of backbone chemotherapy such as fluoropyrimidines (FL), irinotecan (IRI) and oxaliplatin (OXA). We have demonstrated a primary causal effect of *UGT1A1*28* polymorphism on the toxicity of IRI-based treatment, and developed this marker in the clinical setting by re-defining its maximum tolerated dose by genotype-based phase 1b studies, and conducting cost-effectiveness analyses. We also validated the predictive role of *DPYD*-rs3918290, -rs55886062, and -rs67376798 in the development of severe/lethal toxicity after FL treatment in a large group of patients. More exploratory studies are ongoing investigating the predictive/prognostic role of panels of SNPs related to FL, IRI and OXA ADME (cellular transporters, nuclear receptors, and oxidative metabolism), and to patients immunological profile. Based on our data and current pharmacogenetic guidelines, we have set up a clinical pharmacogenetic service. A pharmacogenetic report is embedded in the patient clinical record and a dose adjustment is suggested based on *UGT1A1* and/or *DPYD* risk variants. Among the effects of this experimental service there is a progressive sensitization of the oncologists on pharmacogenetics, demonstrated by the increasing rate of patients referred for pre-treatment genotyping over time.

S07

Pharmacometabolomics-Guided Pharmacogenomics

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Inter-individual variability has been a major hurdle to optimize disease management. It is now the time to implement new working practices to turn information growth into knowledge growth and hence, better informed decisions. Can we delineate inter-individual variability towards differential diagnosis? Can we highlight the disease mechanisms in question to assist disease management? What are the host-microbiome interactions? Do post-dose drug metabolism and safety relate to pre-dose metabotypes and how? This workshop aims to provide an overview and the theoretical background needed for the users/attendees to appreciate the current potential and challenges of applying 'pharmacometabolomics-guided pharmacogenomics' in life sciences. The scope is to generate discussion and interaction among participants. We will look at the advantages of studying the metabolome and inform the genome. We will introduce the hypothesis-generating and -testing pipeline in comparison to hypothesis-directed approaches. Attendees will have hands-on training on state-of-the-art bio- and chem-informatics tools to manage experimental data and shape hypotheses. Selected software will be shown in live action. Main topics covered by the workshop are: (a) hypothesis-generating versus hypothesis-directed approaches, (b) data analysis, (c) targeted, semi-targeted and targeted analytical approaches, (d) (pharmaco-) metabolomics signatures, (e) statistical and pathway analysis, (f) 'discovery-phase genotyping', and (g) data validation.

S08

Making Pharmacogenomics Insights Available at the Point-of-Care

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Pharmacogenomic testing has the potential to improve the safety and efficacy of pharmacotherapy, but clinical application of pharmacogenetic knowledge has remained uncommon. The aim of our work is to design and evaluate a web- and mobile-enabled CDS system for pharmacogenetics-guided drug therapy – the Medication Safety Code (MSC) system – among potential users (i.e., physicians and pharmacists). We deployed an emergent mixed methods design encompassing (1) qualitative interviews with pharmacists and pharmacy students, (2) a survey among pharmacogenomics experts that included both qualitative and quantitative elements and (3) a quantitative survey among physicians and pharmacists. Furthermore, the MSC system was evaluated based on two hypothetical patient scenarios and four follow-up questions on perceived usability. In total, 101 physicians, pharmacists and PGx experts coming from various relevant fields evaluated the MSC system. We found that the MSC system was well-received among the physicians and pharmacists included in this study. A frequent request among participants was to provide specific listings of alternative drugs and concrete dosage instructions. Negligence of other patient-specific factors for choosing the right treatment such as renal function and co-medication was a common concern related to the MSC system, while data privacy and cost-benefit considerations emerged as the participants' major concerns regarding pharmacogenetic testing in general. The results of the card layout evaluation indicate that a gene-centered and tabulated presentation of the patient's pharmacogenomic profile and affected medications is helpful and well-accepted.

S09

Pharmacogenovigilance: Roadmap Your Biomarkers

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Pharmacogenovigilance, defined as pharmacovigilance (PV) activities informed and guided by accompanying pharmacogenomics (PGx) analyses, buttresses the current efforts for rational and mechanistically informed drug design and offers practical advances. Pharmacogenovigilance combined with Big Data offers new ways to rethink biomarker development strategies, so that only the biomarkers that survive testing in real-life are further invested in for personalized healthcare. The cost-effectiveness of such rapid falsification strategies is obvious for pharmaceutical companies. Regarding post-marketing surveillance, pharmacogenovigilance permits the extrapolation of early signals on drug-related events from one population to another, if the worldwide distribution of PGx biomarkers relevant to drug safety/efficacy aspect(s) is known. It, also, helps to understand the pharmacokinetic and pharmacodynamic performance of drugs in population extremes, such as in poor and ultrarapid metabolizers, and can, thus, address dosing regimens, lack of drug efficacy and medication adherence from a population scale overview. Such information, if available, should be included in Periodic Safety Update Reports, Risk Management Plans and Reference Safety Information. The clinical implementation of pharmacogenovigilance over a 7-year period (up to 2012) has revealed genetic variants that affect response to a great variety of drugs and can determine the progression/management of the underlying disease as well as the incidence of adverse drug reactions with obvious societal benefits. The future challenge for pharmacogenovigilance will be to address the interplay of genomic and environmental influences, and it will offer great intervention opportunities for testing hypotheses with regard to disease heterogeneity or mechanisms for variation in drug response under real-life conditions.

S10

In silico Drug Design Methods

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In recent years, pharmaceutical companies have moved away from conducting in-house early-stage preclinical research and are instead partnering with academic institutions to pursue programs on emerging drug targets. This has resulted in significant opportunities for academic-based drug discovery and development centers. The '*in silico* drug design methods' workshop aims to provide an overview and examples of structure-based drug design, including structural biology (X-ray protein crystallography, bioNMR spectroscopy) and modern *in silico* tools (virtual screening, small molecule library preparation). Participants will be able to explore and manage experimental data involving chemical databases, utilizing structural biology information, coupled with computational methods in search for drug leads, explore their challenges and discuss perspectives. Main topics covered by the workshop are: (a) *In silico* drug design in general as a strategy and its various stages; (b) ligand-based and structure-based drug design – the two distinct methods for seeking hit compounds, given the information of the targeted biological system: ligand-based, where no structural information of the protein is provided, and structure-based, where structural features of the protein are used; (c) chem-informatics – handling and filtering of chemical entity databases, based on their chemical or spacial characteristics; (d) virtual screening – the use of large compound libraries of commercially available compounds, in order to obtain several hits targeting a protein of pharmaceutical interest. The overall aim is to provide a theoretical background as well as a hands-on approach on different bio- and chem-informatics software towards drug discovery.

S11

Liquid Biopsy and Individualized Treatment in Cancer

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'Liquid biopsy' has a high potential to give detailed information on tumor genome evolution over time, through simple blood draws that can be used for serial monitoring of the patients. This is a strong advantage towards the classic biopsy approach that does not allow monitoring of primary tumor evolution over time, while sampling of metastatic sites is not always possible for practical reasons. Liquid biopsy has a strong potential to be translated into individualized targeted treatments. The liquid biopsy approach is based on the extraction of molecular information on the primary tumor by analyzing in detail tumor-derived genetic material from: Circulating Tumor Cells (CTC), cell free circulating tumor DNA (ctDNA), circulating miRNAs and exosomes. A variety of analytical systems are continuously being developed for liquid biopsy analysis. Especially molecular assays based on the nucleic acid analysis in CTCs like RT-qPCR, multiplex RT-qPCR, and next-generation sequencing technologies are very powerful since they can be automated and highthroughput. Quality control and standardization in liquid biopsy analysis is very important for the incorporation of this breakthrough concept into prospective clinical trials testing its clinical utility. Especially CTC molecular characterization at the single-cell level holds considerable promise for the identification of therapeutic targets and resistance mechanisms in CTCs as well as for the stratification of patients and real-time monitoring of systemic therapies. This lecture will be mainly focused on the recent advances in the field and its clinical applications in many types of solid cancer.

S12

Evidence-Based Pharmacogenetic Guidelines for Anticancer Treatment

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The Royal Dutch Pharmacists Association (KNMP) is the umbrella organization for both pharmacists and the pharmacy in general. In co-operation with healthcare practitioners the department Drug Information Center creates and maintains guidelines for decision support, such as drug-drug interactions and contraindications. In recent years, the Dutch Pharmacogenetics Working Group (DPWG) of the KNMP has developed evidence-based pharmacogenetic guidelines for 84 gene-drug combinations. These guidelines are updated every 2–3 years. For oncology, guidelines for eight gene-drug combinations have been developed, with therapeutic recommendations for fluorouracil, capecitabine, tegafur, tioguanine, mercaptopurine, irinotecan and tamoxifen. For each selected combination, a systematic PubMed search was first conducted. A risk-analysis was prepared with an overview of key findings from selected articles, accompanied with scores representing the level of scientific evidence and clinical relevance. If possible, dose adjustments were calculated for poor, intermediate or ultra-rapid metabolizers. After approval by the DPWG, the guidelines were distributed using the 'G-Standaard'. This database is incorporated into automated medication surveillance systems in the Netherlands and contains decision-support information for prescribers, community pharmacists and hospital pharmacists. If action is required for a patient with an available genotype, the guideline automatically appears on the computer screen during prescription and dispensing. Importantly, these guidelines are therapeutic (dose) recommendations for patients whose genotypes are available and they do not indicate patients eligible for genotyping. Genotyping will provide better insight in unexplained drug-related problems resulting in improved therapies for these complex patients.

S13

Precision Medicine in Cystic Fibrosis: The Role of Cost of Illness Analyses

M. Macek

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Analysis of health-economic data is of importance for fostering reimbursement of innovative therapies in rare diseases. Currently, health care systems are under strain due to aging population and due to the rapid introduction of novel therapies, exemplified by orphan medicinal products, which bring higher quality of life at increased costs per patient. We have chosen to use long-term data sets generated over the last decade within the Czech national registry, including medical records from Czech health insurance companies to carry out a prevalence-based cost of illness (COI) analysis in a representative set of Czech cystic fibrosis (CF) patients treated at the Prague CF Centre. We analyzed all direct costs associated with CF relative to key CF clinical features and laboratory examinations. Indirect costs were not surveyed due to the retrospective character of the study. A representative cohort of 242 CF patients representing over 60% of all cases in the country was analyzed. Hospital invoices for reference year 2010 were assessed. The mean health care costs were EUR 14,486 per patient, with most of the costs being related to the utilization of antibiotics, antifungals and mucolytics, including medical devices (EUR 10,321). Interestingly, medical procedures (EUR 2,676) and inpatient care (EUR 1,829) were less pronounced. A generalized linear model provided evidence that key cost drivers, for all cost categories, were linked with age and sino-pulmonary disease severity (assessed by the FEV1 spirometric parameter). Chronic *P. aeruginosa* airway infection represented another strong cost driver. Maximum costs were at approximately 16 years of age. COI analysis and regression modelling with the currently available data provided a better understanding of the overall economic burden of CF. COI studies promote health technology assessments regarding the use of new health technologies/interventions, such as in CF the 'CFTR modulating therapies'. A comparison of our results with other studies indicated that although overall costs may be different, spirometric parameter FEV1 can be used as an indicator of the economic impact of CF. Supported by RD-connect.eu

S14

Safety, Feasibility and Cost-Effectiveness of Genotype-Directed Individualized Dosing of Fluoropyrimidines

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Fluoropyrimidines like 5-fluorouracil (5FU) and its oral prodrug capecitabine (CAP) are the cornerstone anti-cancer drugs for multiple types of cancer. Approximately 10–30% of the patients receiving 5FU or CAP experience severe and potentially lethal toxicities. 5FU is extensively metabolized by the enzyme dihydropyrimidine dehydrogenase (DPD) encoded by the gene *DPYD*. There is a strong correlation between reduced DPD activity and increased risk for severe and potentially lethal toxicity following treatment with a normal dose of 5FU. More than 160 genetic variants in *DPYD* have been described. Meta-analyses consistently show that *DPYD**2A, c.2846A>T, *DPYD**13 and c.1236C>G/HapB3 are associated with toxicity. Prospective genotyping for these variants followed by a 25–50% dose reduction or using an alternative drug for patients with 1 or more *DPYD* variants is a safe and (cost)-effective way of reducing fluoropyrimidine-induced toxicity.

S15

Challenges and Opportunities for Measuring the Economic Value of Multi-Gene Tests for Cancer

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Cancer prevention and treatment is being revolutionized by the advent of multi-gene tests – risk assessment panels that include multiple genes and sequencing tests for tumors. These tests can cost thousands of dollars – so an overarching concern is how to assess which tests should be provided and who will pay for them. This lecture will discuss the challenges and opportunities for measuring the economic value of multi-gene tests and the implications for payment policies. These technologies present many challenges: they provide multiple results including those that only provide personal utility or have unknown significance; they may provide secondary findings unrelated to the reason for testing; there is often a lack of data on long-term clinical utility; findings may have interactive effects such that the 'sum is greater than the parts'; and tests for inherited risk may impact family members. I will draw particularly on examples from the research being done by the University of California San Francisco Center for Translational and Policy Research on Personalized Medicine (TRANSPERS). Our Center is focusing on how to address the benefit-risk tradeoffs of new genetic technologies as they move into clinical care and health policy.

S16

The Economics of Cancer Genomics: Is It Cost-Effective?

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Advances in sequencing technology, collectively referred to as next-generation sequencing (NGS) mean that the entire cancer genome (whole genome sequencing) or parts of it (via targeted pan-

els or whole exome sequencing) can now be sequenced in hours and at great depth and increasing sensitivity. However, the widespread translation of NGS technologies into routine cancer diagnostics has been slow. Technical obstacles include ensuring robust bio-informatics, challenges with clinical interpretation, absence of genotype-phenotype databases for cancer, and concern over the costs of NGS to healthcare payers. In particular, there are questions concerning whether results obtained from NGS technologies actually direct clinical management, improve patient outcomes and represent an efficient use of healthcare resources or are just an expensive addition to cancer care. The aim of this presentation is to discuss the available health economic evidence on NGS technologies in cancer (including a cost-effectiveness analysis of a 46 gene cancer panel we conducted in Oxford) and the health economic activities being undertaken as part of the UK 100,000 Genomics Project to assess the cost-effectiveness of whole genome sequencing.

S17

Ubiquitous Pharmacogenomics (the EU Horizon 2020 Project): Making Actionable Pharmacogenomic Data and Effective Treatment Optimization Accessible to Every European Citizen

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Pharmacogenomics (PGx) is the study of genetic variability affecting an individual's response to a drug. Clinical application of pharmacogenomics knowledge will result in less 'trial and error' prescribing and more efficacious, safer and cost-effective drug therapy. However, despite the major advances in PGx and several commercially available PGx tests, its application in routine patient care remains very limited. The Horizon2020 U-PGx project, funded by a 15 million EU grant, is aimed to make actionable pharmacogenomic data and effective treatment optimization accessible to every European citizen. The U-PGx consortium will address major challenges and obstacles for implementation of PGx testing in patient care, taking into account the diversity of healthcare systems and citizens across Europe. Specifically, U-PGx will investigate if the emerging approach of pre-emptive genotyping of an entire panel of important PGx markers is cost-effective and results in a better outcome for patients. A pre-emptive genotyping approach will be employed in a total of 8,000 patients across the EU. With the pre-emptive PGx testing approach, data on multiple important pharmacogenes are collected prospectively and embedded into the patients' electronic record. Typically, it alerts prescribers and pharmacists through electronic clinical decision support systems when a drug is ordered or dispensed for a patient with an at-risk genotype. The new model of personalized medicine through pre-emptive PGx-testing will be conducted at a large scale in seven existing European health care environments (The Netherlands, Spain, UK, Italy, Austria, Greece, Slovenia).

S18

Cancer Pharmacogenomics – The Way Beyond

M. Schwab

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Variation in drug disposition and response among patients is a major concern associated with many therapeutic agents used in all disciplines of medicine, particularly in oncology. The clinical relevance of interindividual variability is most evident with drugs that have a narrow therapeutic window (i.e., the dose used is close to the dose probably resulting in drug-related toxicity in most individuals). With increasing information available from the Human Genome Project, pharmacogenomics (PGx) aims to elucidate the genomic determinants of drug efficacy and toxicity. Variation of drug response, however, is caused by a combination of genetic and environmental factors as well as patient characteristics which can affect the pharmacokinetics and/or pharmacodynamics of drugs. PGx research has led to fundamental discoveries, and a large resource of PGx traits has been generated in which variation in the gene sequence and/or variation in gene expression of ADME targets such as drug-metabolizing enzymes, drug transporters and nuclear receptors are associated with alterations in drug response. For instance clinical important cancer drugs related to PGx are thiopurines, tamoxifen, methotrexate, irinotecan etc. However, a more comprehensive approach is required to consider PGx in entire biological and pharmacological pathways. The combination of recently developed *-omics* approaches, like epigenomics (e.g., DNA methylation, miRNA) and metabonomics, together with integrative and holistic systems and pharmacology strategies are highly promising for the identification of novel putative ADME targets for better prediction of drug response.

S19

Pharmacogenomic and Epigenomic Biomarkers for Prediction of Drug Response

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There are pronounced interindividual variations in drug metabolism, drug response and incidence of adverse drug reactions. In addition to genetic variation, epigenetic and long non-coding (lncRNA) dependent regulation of these genes is important and future direction in this novel research field is outlined with respect to our understanding of interindividual differences in drug action [Ivanov et al., 2012]. A novel class of drugs, so called epidrugs, are known to can intervene in the epigenetic control of gene expression for disease treatment, and many so-called epidrugs are now in clinical development. In addition, disease diagnosis prognosis and drug treatment success can be monitored by epigenetic biomarkers. Regarding the genetic variation it is clear that in addition to common previously characterized variations of importance for drug response, which are frequently utilized for current therapy,

there are also a huge number of rare gene variants of importance for the individual response worth attention. Indeed studies in monozygotic and dizygotic twins as well as analyses of large whole genome and whole exome sequencing projects reveal that only about 50–70% of the true interindividual variation in drug pharmacokinetics can be assigned to known mutations commonly analyzed for. The lecture will give an update in the field of current and future genomic biomarkers, epigenomic alterations during development and epigenetic mechanisms of importance for prediction of drug metabolism, drug action and ADRs focusing on the most clinically relevant examples.

S20

Brachyury Identifies a Class of Enteroendocrine Cells in Normal Human Small Intestinal and Colonic Crypts

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Normal homeostasis of adult intestinal epithelium and repair following tissue damage is maintained by a balance of stem and differentiated cells, many of which are still only poorly characterised. Enteroendocrine cells of the gut are a small population of differentiated, secretory cells that are critical for integrating nutrient sensing with metabolic responses, dispersed amongst other epithelial cells. Recent evidence suggests that sub-sets of secretory enteroendocrine cells can act as reserve stem cells. Given the link between cells with stem-like properties and cancer, it is important that we identify factors that might provide a bridge between the two. Here, we identify a sub-set of chromogranin A-positive enteroendocrine cells that are positive for the developmental and cancer-associated transcription factor Brachyury in normal human small intestinal and colonic crypts. Whilst chromogranin A-positive enteroendocrine cells are also Brachyury-positive in colorectal tumours, expression of Brachyury becomes more diffuse in these samples, suggesting a more widespread function in cancer. The finding of the developmental transcription factor Brachyury in normal adult human intestinal crypts may extend the functional complexity of enteroendocrine cells and serves as a platform for assessment of the molecular processes of intestinal homeostasis that underpins our understanding of human health, cancer and aging.

S21

A Tumor-Genetic Signature of Patients' Prognosis and Response to a Platinum-Based Treatment in High-Grade Ovarian Cancer

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Recurrent somatic mutations, outside TP53, are at low prevalence in high-grade epithelial ovarian cancers. This is a retrospective analysis conducted to pursue a predictive or prognostic value of a pattern of somatic mutations identified in 79 patients first-line treated with a platinum-based regimen after primary surgery, for high-grade chemo-naïve epithelial ovarian cancer. For the next-generation sequencing analysis we used a 26 genes panel TruSight Tumor kit. The clinical endpoints were platinum-free interval (PFI), disease-free survival (DFS) and overall survival (OS). Genetic mutations were found in *TP53*, *APC*, *BRAF*, *FBXW7*, *KRAS*, *PIK3CA*, and *PTEN* genes. Patients who were carriers of somatic mutations in more than one gene were at higher risk of treatment failure due to tumor progression or death. Median PFI was 4.10, 8.69 and 28.23 months in patients with 2, 1, or no mutated genes, respectively (log-rank $p = 0.0081$). Median DFS was 10.23, 14.29 and 27.80 months, respectively ($p = 0.0098$), and OS was 32.59, 48.00 and 95.80 months ($p = 0.0157$). Using The Cancer Genome Atlas dataset, we were able to replicate a similar effect on patients' OS. This study highlights a tumor-genetic signature identifying patients with an extremely poor prognosis. Possible therapeutic alternative could be proposed for these patients targeting the detrimental mutations identified.

S22

miR-328 Targets Histone H2AX and Regulates Lung Cancer Cells

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Increasing number of reports indicate that microRNAs play a key role in cell growth, differentiation, and apoptosis. In this study, we describe how the regulation of miRNA-328 (miR-328), which increases in cancer cells, is involved in the apoptosis of lung cancer cells (A549 and NCI-H1650). Expression analysis has verified that the level of miR-328 is significantly decreased in apoptotic A549 and NCI-H1650 cells. Furthermore, overexpression of miR-328 in

lung cancer cells inhibits etoposide-induced cellular apoptosis. Additionally, we identified that histone H2AX is a downstream target of miR-328, which can bind directly to the 3′-untranslated region (3′-UTR) of H2AX, subsequently downregulating both the mRNA and protein levels of H2AX. The results from co-expression demonstrated that overexpression of H2AX which lacked 3′-UTR in A549 and NCI-H1650 cells partially reduces the effect of miR-328 on cell apoptosis. Taken together, our results illuminate that miR-328 functions as an apoptosis silencer to regulate lung cancer cell apoptosis through targeting histone H2AX and may become a critical therapeutic target in lung cancer.

S23

The Intracellular Localization of Serotonin Transporter as Candidate Biomarkers for the Prediction of Antidepressant Response

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Introduction: The need for personalized antidepressant therapy is increasing. Every third depression patient does not respond to the first prescribed medication. The individual likelihood to show a good response is to date difficult to predict, and the choice of a drug prescription is rather fitted to the individual expected side effects than to the expected response profile. This aroused the need for biomarkers that can predict in advance the individual response and help in developing individually tailored therapy. Inhibition of serotonin transporter SERT is a key mechanism of many antidepressants. It has been shown that SERT re-localizes from the cytoplasmic membrane upon incubation with antidepressants. We are assessing this internalization of SERT as a functional biomarker of drug action in lymphoblastoid cell lines (LCLs) derived from depression patients. **Methods:** Patients were recruited in the MARS clinical study at the Max-Planck Institute, Munich. Clinical interventions and responses were documented. Blood samples were taken for conducting pharmacogenomic tests. SERT localization is determined by labeling with antibodies against an extracellular epitope. LCLs are incubated with antidepressants or with vehicle (controls) and are fixed. Samples will either undergo permeabilization or not. In non-permeabilized cells antibodies will bind with SERT molecules localized at the cytoplasmic membrane. In permeabilized cells antibodies will bind internalized and membrane-located molecules. Non-/permeabilized samples are compared with each other from responding and non-responding patients using flow cytometry. **Conclusion:** The existence of differences in SERT cellular localization between patients with different response profiles would give a new dimension in the prognosis of therapeutic response.

S24

Genetic Markers of Huerthle Cell Neoplasms

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Introduction: Huerthle cell neoplasms are regarded as a rare subtype of follicular thyroid tumours. At present, the definitive way to differentiate a benign Huerthle cell thyroid adenoma (HCTA) and Huerthle cell thyroid nodule (HCTN) from Hurthle cell thyroid carcinoma (HCTC) is based on histological examination of thyroid tissue. The aim of our study was to search for possible genetic markers for early distinction between HCTA and HCTN from HCTC and for early prediction of recurrent or metastatic disease. **Patients and Methods:** A retrospective study included 139 patients treated by thyroid surgery for Huerthle cell neoplasm. Clinical records and tumor histopathology of the patients were retrospectively reviewed. Genomic DNA was isolated from FFPE samples of tumour and normal thyroid tissue. Ion Torrent AmpliSeq cancer panel was used to screen for 739 mutations in 46 cancer-associated genes in 10 representative tumour DNA samples. Next, specific mutations were analysed in all tumour samples using high sensitivity RT-PCR and confirmational Sanger sequencing. Analysis of DNA samples from normal thyroid tissue was used to confirm their somatic origin. **Results:** Patients were diagnosed by histopathology as follows: 53 had HCTC, 37 HCTA, 21 HCTN and 18 had multinodular goiter, or follicular thyroid adenoma, or lymphocytic thyroiditis. Among HCTC patients, 16 had recurrent and 20 metastatic disease. The HCTC patients had a different gender (F/M) ratio ($p = 0.043$), were older ($p = 0.004$) and had a larger initial tumour diameter.

S25

Genomic Variants in the *SLCO1B3* Gene May Serve as Pharmacogenomic Biomarkers upon Cancer Drug Administration

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Pharmacogenomics explores drug response variability via the analysis of genomic profiles. Genomic variants in drug transporters and drug-metabolizing enzymes have been associated with pharmacokinetic and/or pharmacogenomic profiles that differ among individuals. *SLCO1B3* encodes a solute carrier organic anion influx transporter member, which is involved in the uptake of a broad range of drug substrates, including anti-cancer drugs. Whole-genome sequencing comes to help identifying putatively causative and novel genomic variants, affecting both the function and the structure of a large number of pharmacogenes. Based on the findings of Mizzi and coworkers [Pharmacogenomics 2014;15:

1223–1234], we validated two variants of the *SLCO1B3* gene, residing at its 5′UTR region (rs527574433 and rs71581943) in 57 healthy individuals. For this, a PCR-based Sanger sequencing methodology was developed, optimized and applied. Our findings indicate population frequencies of 35% (rs527574433) and 14% (rs71581943) in the Hellenic population, respectively, in agreement with the findings of Mizzi and coworkers [2014]. Functional studies are needed to ascertain whether these variants constitute pharmacogenomic biomarkers for anti-cancer treatment.

S26

Current Views and Knowledge of Drug Prescribers on Pharmacogenomics and Its Role in Patient-Tailored Treatment

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Pharmacogenomics explores inter-individual variability upon drug administration on the basis of genomic profiles. Although the benefits of genomic information in the clinic and the public health system become evident, Greece suffers from a substantial lack of genomics awareness [Mai et al., 2011, 2014]. We created a questionnaire addressed to health professionals with a dual purpose: (a) Firstly, we wanted them to acquire a first contact with the concept of 'genetic test' and its use in every-day practice, and (b) Secondly, we wanted to understand their level of pharmacogenomics knowledge in order to use this information as a base to properly configure education seminars. Our ultimate goal is to educate and train health professionals towards pharmacogenomics implementation in the clinic. As a result, not only will the quality of health service be raised, because we will have an optimal treatment response, but this will also lead to budget savings in public health, especially in diseases and treatments that have already been associated with certain genes (pharmacogenes).

S27

A Preemptive Pharmacogenomics Strategy to Tailor-Made Therapeutics against Cancer: The U-PGx Paradigm

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Inter-individual variability following drug administration is currently a major hurdle in disease management. Preemptive pharmacogenomics are the means towards personalized diagnostics and tailor-made therapeutics. Genomic variations in genes which encode drug transporters or drug metabolizing enzymes (pharmacogenes) affect drug pharmacokinetic and pharmacodynamics properties, accompanied by toxicity and limited efficacy. Today, several genomic variations have been identified to affect the efficacy and safety of anticancer drugs. Herein, we will apply preemptive pharmacogenomics to cancer patients not only to optimize drug administration, but also to identify biological mechanisms that serve as new drug targets. The Ubiquitous Pharmacogenomics (U-PGx) project is the first clinical trial of pharmacogenomics in Europe in order to prove the importance of pharmacogenomics in clinical practice. We will focus on pharmacogenes *(CYP2D6, CYP2C19, TPMT, DPD, UGT1A1)* upon anticancer drug administration (tamoxifen, esomeprazole, lansoprazole, pantoprazole, irinotecan). Clinical implementation and cost effectiveness will be further explored.

S28

Comparative Study and Meta-Analysis of Meta-Analysis Studies for the Correlation of Genomic Markers with Early Cancer Detection

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A large number of common disorders, including cancer, have complex genetic traits, with multiple genetic and environmental components contributing to susceptibility. A literature search revealed that even among several meta-analyses, there were ambiguous results and conclusions. In the current study, we conducted a thorough meta-analysis gathering the published meta-analysis studies, previously reported to correlate any random effect or predictive value of genome variations in certain genes for various types of cancer. The overall analysis was initially aimed to result in associations (i) among genes which when mutated lead to different types of cancer (e.g. common metabolic pathways) and (ii) between groups of genes and types of cancer. We have meta-analysed 150 meta-analysis articles which included 4,474 studies, 2,452,510 cases, 3,091,626 controls (5,544,068 individuals in total) including various racial groups, and other population groups (native Americans, Latinos, Aborigines etc.). Our results were not only consistent with previously published literature but also depicted novel correlations of genes with new cancer types. Our analysis revealed 17 gene-disease pairs that are affected and generated genes/disease clusters, many of which prove to be independent of criteria used, which suggests that these clusters are biologically meaningful.

S29

Identification of Cancer Predisposition Variants in Apparently Healthy Individuals Using a Next-Generation Sequencing-Based Family Genomics Approach

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Cancer, like many common disorders, has a complex etiology, often with a strong genetic component and with multiple environmental factors contributing to susceptibility. A considerable number of genomic variants have been previously reported to be causative of, or associated with, an increased risk for various types of cancer. Here, we adopted a next-generation sequencing approach in 11 members of two families of Greek descent to identify all genomic variants with the potential to predispose family members to cancer. Cross-comparison with data from the Human Gene Mutation Database identified a total of 571 variants, from which 47% were disease-associated polymorphisms, 26% disease-associated polymorphisms with additional supporting functional evidence, 19% functional polymorphisms with in vitro/laboratory or in vivo supporting evidence but no known disease association, 4% putative disease-causing mutations but with some residual doubt as to their pathological significance and 3% disease-causing mutations. Subsequent analysis, focused on the latter variant class most likely to be involved in cancer predisposition, revealed two variants of prime interest, namely *MSH2* c.2732T>A (p. L911R) and *BRCA1* c.2955delC, the first of which is novel. *KMT2D* c.13895delC and c.1940C>A variants are additionally reported as incidental findings. The next-generation sequencing-based family genomics approach described herein has the potential to be applied to other types of complex genetic disorder in order to identify variants of potential pathological significance.

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