Pharmacogenomics and Genomic Medicine:

Bridging Research and the Clinic

BOOK OF ABSTRACTS

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Pharmacogenomics and Genomic Medicine:

Bridging Research and the Clinic

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Effy Vayena is a senior research fellow at the Institute of Biomedical Ethics (IBME), University of Zurich and the academic coordinator of the PhD program in Biomedical Ethics and Law/medical track. Before joining the IBME she worked for several years at the World Health Organization headquarters where she was involved with the Organization's activities on research ethics, and reproductive health research. She has served as a member of the WHO's Research Ethics Review committee and she continues consulting for the Organization.

She has published on the ethics of health research, on issues surrounding assisted reproductive technologies, biobanks, pediatric research, genomics and research with online health data. Her current research focus is on ethical and policy issues that arise in the areas of genomics (including direct-to-consumer genomics), personalized medicine, the novel uses of online health data for research, data –sharing for health research and health research led by participants.

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Professor Milan Macek Jr. MD, DSc is the chairman of the largest academic medical / molecular genetics institution in the Czech Republic, which also comprises a research / diagnostics reproductive genetics centre /ublg.lf2.cuni.cz/. He is also the Vice President of the European Society of Human Genetics (www.eshg.org), board member of the European Society for Human Reproduction and Embryology (ESHRE.com) and of the European Cystic Fibrosis Society (ECFS.eu). His institute is a "clearing centre" for dissemination of knowledge in genetics gathered within various international European projects, such as CF Thematic Network, EuroGentest, EuroCareCF or Techgene, to Central and Eastern Europe. Prof. Macek did his first post-doc at the Institute of Human Genetics in Berlin, continued as a postdoctoral fellow at the McKusick-Nathans Centre for Genetic Medicine, Johns Hopkins University in Baltimore and during that time he was also a fellow at Harvard School of Medicine in Boston. He was the local host of the 1995 HUGO Mutation Detection Course in Brno, the 2005 European Society of Human Genetics conference and of the 2008 European Cystic Fibrosis Conference, both held in Prague. Prof. Macek is national coordinator of Orphanet (www.orpha.net), active member of Eurogentest (www.eurogentest.org), has been the chief advisor of the Czech EU Council Presidency under which the "EU Council recommendation on an action in the field of rare diseases" was adopted in June 2009. He also serves at the EUCERD.eu committee on rare diseases.

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George Patrinos obtained his PhD in Molecular Biology and Genetics from the University of Athens (Greece). He currently serves as Associate Professor of Pharmacogenomics and Pharmaceutical Biotechnology in the University of Patras, Department of Pharmacy (Greece). Also, he is Greece's National representative in the CHMP Pharmacogenomics working party of the European Medicines Agency (EMA, London, UK), member of the International Rare Disease Research Consortium (IRDiRC) and Scientific Director of the Golden Helix Foundation (London, UK). His research interests involve pharmacogenomics for hemoglobinopathies and neuropsychiatric disorders, transcriptional regulation of human fetal globin genes and genotype-phenotype correlation in human genetic disorders. His group is also internationally recognized for its involvement in developing National/Ethnic Genetic databases to document the genetic heterogeneity in different populations worldwide, while he also has a keen interest in public health genomics to critically assess the impact of genomics to society and public health. George has more than 130 publications in peer-reviewed scientific journals and textbooks, some of them in leading scientific journals, such as *Nature Genetics*, *Nature Rev Genet*, *Nucleic Acids Res*, *Genes Dev*, and he is the Editor of the textbook "Molecular Diagnostics", published by Academic Press, now in its 2nd edition. Furthermore, he serves as Communicating Editor for "*Human Mutation*" and member of the editorial board of several scientific journals. He has been a member of several international boards and advisory and evaluation committees and he is the co-organizer of the international meeting series "Golden Helix Symposia" and "Golden Helix Pharmacogenomics Days". He has given numerous keynote and plenary lectures in international conferences as invited speaker and his research projects received funding of over 6M EUR from national and international funding agencies.

INVITED SPEAKERS

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Emmanouil Dermitzakis is currently a Louis-Jeantet Professor of Genetics in the Department of Genetic Medicine and Development of the University of Geneva Medical School. He is a member of the executive board of the Institute of Genetics and Genomics in Geneva (iGE3) and is also an affiliated Faculty member at the Biomedical Research Foundation of the Academy of Athens in Greece. His current research focuses on the genetic basis of cellular phenotypes and complex traits. He has authored and coauthored more than 120 papers in peer-reviewed journals and many of them in journals such as Nature, Science and Nature Genetics. His papers have been cited more than 23000 times and his H-index is 56. His research is supported by the Louis-Jeantet Foundation, the Wellcome Trust, the Swiss National Science Foundation, the European Commission, the Juvenile Diabetes Foundation and the US National Institutes of Health (NIH). He is also the recipient of a European Research Council (ERC) grant. He has been invited to give talks and keynote lectures in most of the prestigious genetics meeting and is the organizer of training courses including the Wellcome Trust HapMap course and founder and organizer of the Leena Peltonen School of Human Genomics. He is currently an analysis co-chair in the GTex project and has served as an analysis co-chair in the pilot phase of the ENCODE (ENCyclopedia Of Dna Elements) consortium and member of the analysis group of the Mouse Genome Sequencing Consortium and the International HapMap project. He had a leading analysis role in the HapMap3 project and is a member of the analysis group of the 1000 genomes project. He has served in the Board of Reviewing Editors of Science (2006-2011), and as a Senior Editor in PLoS Genetics (2006-2012) and is currently a member of

the Board of Reviewing editors for the new scientific journal eLIFE. He is also in the advisory board of DNAnexus.

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Vita Dolžan, MD PhD received her degree in medicine, as well as MSc and PhD degree in Biochemistry and Molecular biology at the Faculty of Medicine, University of Ljubljana. In 2000 - 2001 she was a postdoctoral fellow with Prof Magnus Ingelman-Sundberg at Karolinska Institute, Stockholm. Currently she is a Full Professor of Biochemistry and Molecular Biology at the Faculty of Medicine, University of Ljubljana (UL MF). She is also the founder and Head of the Pharmacogenetics Laboratory at the Institute of Biochemistry, UL MF. Her research interests are focused on applied research in the field of pharmacogenetics and on implementation of novel molecular biology based methods into clinical use. She published over 65 research papers that have been cited over 2000 times. She is a member of the Genomic Medicine Alliance, European Research Network on Pharmacogenetics/genomics and a member of the Clinical Pharmacogenetics Implementation Consortium (CPIC).

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I qualified as a Pharmacist in 1983 at the Philipps University, Marburg, Germany. I then pursued my PhD studies in Pharmacology at Cologne University, Cologne, Germany, where I obtained my degree (Dr. rer. Nat) in 1985. I then proceeded to do Postdoctoral Training with Bayer AG/University of Cologne before moving to Saudi Arabia in 1987. Since then I have been working in cardiovascular research at King Faisal Specialist Hospital and Research Centre, where I am currently heading the Cardiovascular and Pharmacogenomics Research and Personalized Medicine programs of the Hospital. My research interests focus on the genetics and mechanisms of complex cardiovascular diseases and therapy thereof. Specifically, my lab is interested in understanding the role of the untranslated and non-coding regions of genes in complex disease pathways.

Maurizio Ferrari

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present his research is focused on the development of diagnostic tests with the application of the next generation sequencing. He is author of 849 publications: 246 in peer reviewed journals, 67 in other journals, 1 book, 45 book chapters and 490 abstracts at International and National Congress with a total I.F. 1113,83; h-index: 42 (scholar Google); citations: 8846 and i-10 index: 131.

Ivo Gut

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Ivo Gut is a Director of the Centro Nacional de Análisis Genómico (CNAG) in Barcelona, one of the largest European genome sequencing operations, which he established in 2010. He is author of more than 160 research papers, 11 reviews and 12 book chapters, cited over 14 000 times. His research interests are genomics, genetics, high-throughput nucleic acid analysis methods, proteomics, implementation of –omics methods, omics technologies, automation bioinformatics, data analysis, disease gene identification, cancer, agrogenomics. He has more than 20 years experience in high-throughput nucleic analysis (genotyping and sequencing DNA, RNA and DNA methylation), technology development in nucleic acid and protein analysis. He was promoted at the Centre National de Génotypage (CNG) – CEA (1999-2009) from Head of Technology Development to Associate Director, where he established with his team the highest throughput genotyping platform in Europe and executed many genome-wide association studies, he initiated and was the coordinator of the EU-funded Project READNA in which 2nd, 3rd and 4th generation nucleic acid analysis technologies were developed. He received his PhD in Physical Chemistry from the University of Basel in 1990. After his appointments as Research Fellow at Harward Medical

School and at Imperial Cancer Research Foundation of London, he led a group in the Department for Vertebrate Genomics at Max-Planck-Institute for Molecular Genetics. He is inventor of 25 patents or patent applications, founder of 4 biotech start-ups, and serves on numerous international advisory boards.

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Evgenia Kartsaki is a SW engineer in Pharmacogenomics Group, within Bioinformatics Laboratory at the Institute of Computer Science, Foundation for Research and Technology-Hellas (FORTH). She studied Computer Science at the University of Crete with majoring in Bioinformatics. For her B.Sc. thesis she implemented a system that matches signaling pathways (KEGG) that correlate with gene-expression profiles. Furthermore, she worked on a project about Bio-Knowledgeable Gene Markers: Combining Mircroarrays and Gene Regulatory Networks. During her undergraduate studies, she studied at the Polytechnic University of Catalonia for a semester and she did an internship related to SEO, SEA, Social media and Affiliate Marketing at the company TennisPlanet. Her research interests include Bioinformatics, Data Mining and Machine Learning.

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Dr. Katsila currently serves as a senior research fellow in the Pharmacogenomics and Personalized Medicine group in the University of Patras, Greece. She obtained her PhD in Chemistry from the University of Patras (Greece) and the Biomedical Research Foundation of the Academy of Athens (Greece). She holds a MSc in Clinical Biochemistry and Molecular Diagnostics (University of Athens, Greece) and a BSc in Biochemistry with a year in industry/research (Imperial College London, UK).

Dr. Katsila has acquired a multidisciplinary expertise, investigating the underlying molecular mechanisms of disease (cancer, inflammation) or focusing on drug research and development (Merck Sharp & Dohme Research Laboratories, UK) and more recently, biomarkers (cancer secretome) and personalized medicine. She has developed substantial *in vivo* (rodents, primates) and *in vitro* skills (molecular and cell biology techniques, mass spectrometry approaches). Her pre-doctoral work resulted in 7 peer-reviewed publications, 5 of them as a first author. Dr. Katsila was the VHIO's lead scientist in the effort aimed at the modeling and predicting resistance to molecular therapies in colorectal cancer (COLTHERES). She is an EACR ambassador and an Associate of the Royal College of Science (UK).
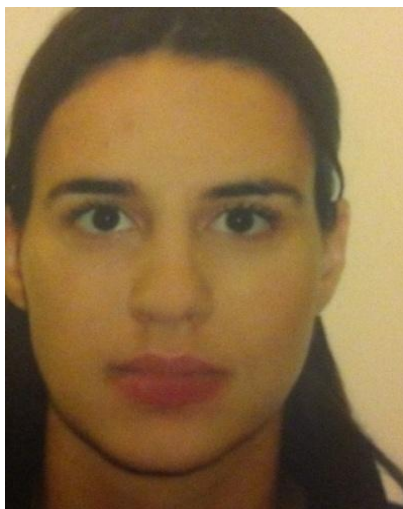
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Sotiria Kechagia is a lawyer specialized in Intellectual Property Law and Bioethics. She graduated from Athens Law School. Then she worked as a Laywer Trainee in Athens and became a Certified Lawyer at the Athens Bar Association. She holds an LLM on Intellectual Property Law at Queen Mary, University of London sponsored by the Greek Foundation of State Sponsorships (I.K.Y.). Her LLM thesis was on *Biobanking and other current issues regarding the use of biological material in medical research*. For two years she worked as a researcher at Queen Mary on the licensing of copyrighted material on the Internet. Then she worked at the Law School of the University of Geneva on a UNESCO-EU funded programme on recommendations regarding *the prevention and fight of the illicit trafficking of cultural goods in Europe*. Currently, she works at the Department of Genetic Medicine and Development at the the University of Geneva Medical School doing research on Ethical, Legal, Social Issues regarding Genetic and Genomic research.

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Judit Kumuthini is currently the Bioinformatics Human Capital Development Manager at the Centre for Proteomic and Genomic Research (CPGR) based in Cape Town, South Africa. Prior to that, she rolled out the Bioinformatics service platform from inception at the CPGR and was the Bioinformatics manager for over 5 years. Her initial tertiary education commenced with Hons invBiomedical Sciences at University of Westminister, London and specialised in Bioinformatics and obtained an MSc in this discipline from the University of Abertay, Dundee, Scotland followed by a PhD from Cranfield University, UK. The knowledge, skills and expertise gained in Bioinformatics, combined with over six years of managerial and technical experience, is applied in her commitment to developing Bioinformatics capacity both in South Africa and throughout the African continent. In addition, Judit is a Co-Principal Investigator on an NIH funded H3ABioNet (H3A pan African Bioinformatics Network) project. In this role, she is tasked with supporting and leading her team to provide bioinformatics expertise to life scientists in personalized medicine, addressing a wide range of biological questions from genomics to systems biology in Human Hereditary and Health.

Judit is well connected with key local and international bioinformatics stakeholders through active involvement in various networks, societies, initiatives, projects and interest groups. She is committed to developing local capacity in the field of bioinformatics and computational biology in Africa, specifically in South Africa. She has successfully supervised many postgraduate students at various levels over the years at Cranfield University, University of Western Cape (UWC), Stellenbosch University (US) and University of Cape Town (UCT). Her broad research interests include personalized medicine and

pharmacogenomics, information management and knowledge extraction, standardization in bioinformatics and e-learning.

Kleanthi Lakiotaki

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Kleanthi Lakiotaki is a post-doc researcher in Pharmacogenomics Group, within Bioinformatics Laboratory, at Institute of Computer Science-Foundation for Research and Technology Hellas (FORTH). She studied Physics at the University of Crete with majoring in Atomic - Molecular Physics and she also completed an MRes course at the same University. During her studies there, she was an undergraduate and postgraduate fellow at FORTH. She has also been a Marie Curie research fellow at Imperial College London. She holds a PhD degree in Information and Decision Sciences from Universite Paris Dauphine and Technical University of Crete, under a joint supervision framework. During her PhD studies she was funded by the General Secretariat for Research and Technology in Greece. She has been author or co-author of 28 journal articles, book sections and peer reviewed conference articles. She has been teaching at university level courses such as E-business, Business Intelligence and Knowledge Management, Object Oriented Programming, Decision Support Systems and Statistics. Her research interests include Bioinformatics, Recommender Systems, Data Mining and Machine Learning.

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Ming Ta Michael Lee graduated from the University of Toronto in 1998 with a B.Sc. degree in Medical Genetics. He then obtained his PhD in Virology from the University of Cambridge in 2002. Afterwards, he joined Dr. Bryan Cullen's lab as a Research Associate at Howard Hughes Medical Institute at Duke University Medical Center working on HIV. He then joined Dr. Yuan-Tsong Chen's lab as a postdoc at Institute of Biomedical Sciences, Academia Sinica in Sept 2003 and was promoted to assistant director at the National Center for Genome Medicine (NCGM) from April 2004 and as Assistant Research Scientist in 2008 at the Institute of Biomedical Sciences, Academia Sinica. In Sept 2012, he joined Center for Genomic Medicine at RIKEN as Team Leader of Laboratory for International Alliance on Genomic Research.

He has been involved in various genetic studies from rare diseases, complex diseases and Pharmacogenetics. He is also involved in various international consortia aiming to advancing the genetics field. The goal of his research is to identify useful biomarkers which can be used clinically with the ultimate goal of establishing "Personalized Medicine"

Max van Min

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Max van Min is CEO of Cergentis and co-inventor of its Targeted Locus Amplification (TLA) Technology. Max received a Master of Science degree in Biotechnology from Wageningen University & Research Centre in the Netherlands and has a career in commercial management positions in the Life Sciences.

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Clint graduated with a B.Sc. (Hons) in IT in 2007, specializing in Computer Science and Artificial Intelligence. He then spent 3 years working as a software developer in MITA (Malta Information Technology Agency), where he was involved in whole software lifecycle in national projects related to Transport Malta and the Maltese Courts of Justice.

In 2010 he obtained an M.Sc. in Bioinformatics, with a distinction, from King's College in London. He is currently employed as a Research Support Officer II with the University of Malta, where he is also currently reading for his Ph.D., in collaboration with Rotterdam Erasmus University.

His research focuses on the analysis of mixed DNA Pools and Whole Genomes in relation to population studies and genomic medicine.
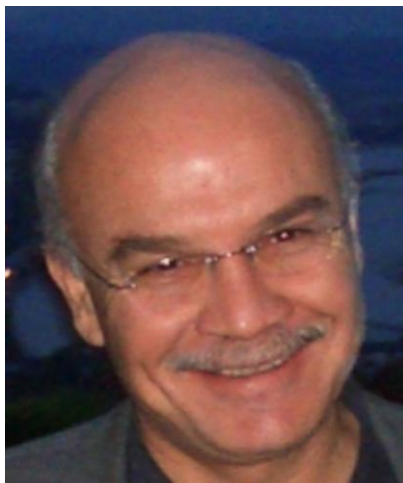
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George Potamias is a Principal Researcher at FORTH's Institute of Computer Science. For a number of years he was also an adjunct professor at the Dept. of Computer Science, University of Crete, Heraklion, Crete, Greece. Dr. Potamias earned his PhD from the University of Patras, in the area of Artificial Intelligence and Knowledge-based systems. He has been working in the field of knowledge-based systems, machine learning and data-mining for over 15 years, with a number of publications to his credit, and active involvement in more than 20 EU-funded projects. In the last ten years his R&D interests and activities focus on the areas of Biomedical Informatics and Bioinformatics, with active involvement in several related R&D FP7 projects, e.g., ACGT (Advancing Clinico-Genomic Trials on cancer; www.eu-acgt.org), LOCCANDIA (Lab On–Chip based protein profiling for CANcer DIAgnosis; www.loccandia.eu), GEN2PHEN (Genotype to Phenotype Databases – A Holistic Approach; www.gen2phen.org), and ENCCA (European Network for Cancer research in Children and Adolescents). Currently he is leading on behalf of ICS-FORTH the Greek-funded eMoDiA (electronic Molecular Diagnostics Assistant) project.

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Olaf Riess obtained his MD from the Humboldt University Berlin, Charité Hospital (Germany). Having obtained an MRC Canada fellowship he spend a 2 years postdoc in the lab of Michael Hayden, Vancouver, Canada, working on Huntington's disease. After receiving his Habilitation from the Ruhr-University of Bochum he became the Director of the Department of Medical Genetics in Rostock (Germany) and is now full Professor and Director of the Institute of Medical Genetics and Applied Genomics, University of Tübingen (Germany) and founder of the Rare Disease Center Tübingen. He serves at several scientific and governmental advisory boards, such as a member of the task force on a national plan for rare diseases of the German Ministry of Health (BfG, NAMSE), as a board member of the study section Neuroscience (Fachgutachter) of the German Research Foundation, an associated member of the Commission on genetic diagnostics (Gendiagnostik-Kommission) of the German Ministry of Health (BfG) and as a board member of the International Rare Disease Research Consortium IRDiRC. At the University he served as Dean of Research at the Medical Faculty and later as Dean of International Affairs. He is currently serving as Senator at the University. His research interest is on neurodegenerative diseases such as ataxias, Parkinson disease, Huntington disease and Dystonia, but also on intellectual disability and cancer. For neurodegenerative diseases his group developed and characterized more than 30 different mouse and rat models which are now being used to study genetic modifiers and serve as models for preclinical treatment studies. His current interest is on the role of Medical Genetics in clinical guiding applying the newest next generation sequencing technologies in cancer and in the discovery of novel genes. Olaf Riess has published close to 300 publications and is author of several genetic books or book

chapters. He serves in editorial boards of several scientific journals. Olaf Riess is or was coordinating several European research networks such as Neuromics, RATstream or EUROSCA.

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Prof. Dr. Ron van Schaik, PhD is a registered European specialist Laboratory medicine (2003) and a Full Professor of Pharmacogenetics (2013). He is working at the Dept. Clinical Chemistry at the Erasmus University Medical Center Rotterdam, The Netherlands. He is Director of the International (IFCC) Reference Center for Pharmacogenetics and he leads the Unit Research & Development of the Dept. Clinical Chemistry. He is also responsible for laboratory testing in Emergency Medicine and Cardiology, and is involved in development of new prostate cancer biomarkers.

His research focuses on clinical implementation of Pharmacogenetics. Specific targets are Transplantation/immunosuppression (cyclosporin, tacrolimus, MMF), Oncology (paclitaxel, docetaxel, tamoxifen), Pain (morphine, tramadol), Psychiatry (antidepressants, antipsychotics), HIV (efavirenz, nevirapine) and Anticoagulation (coumarins). He has published over 175 articles in this field of pharmacogenetics. Prof van Schaik participated in 12 grants with a total value of € 7,8 million.

Prof van Schaik has given over 200 invited lectures. He participates in national and international advisory committees on pharmacogenetics, a.o. IFCC Task Force Pharmacogenetics (Chair), IATDMCT Pharmacogenetics Committee (chair), Dutch Task

Force Pharmacogenetics (NVKC; chair), Dutch Committee on Molecular Biological Diagnostics (CMBD; chair), IUPHAR working group Pharmacogenetics (member), European Pharmacogenetics Research Network (Steering Committee), European Society for Personalized Medicine (EUSPM; treasurer), European Society for Pharmacogenetics and Theranostics (ESPT; Chair Scientific & Clinical Implementation Division), AACC Personalized Medicine Division (founding member) and the Pharmacogenetics Working Group of the European Medicine Agency (EMA). In 2001, he received the Ortho Clinical Diagnostics Award for Outstanding Research, in 2009 the AACC Outstanding Speaker Award, and in 2010 the AACC/Mol Pathology Award for Outstanding Scientific Research.

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Dr. Alessio Squassina has held a position of Post Doctoral research fellow at the Department of Biomedical Sciences of the University of Cagliari, Italy, since 2012. He studied biology at the University of Cagliari, Italy and trained as a pharmacologist and molecular biologist in Italy (University of Cagliari) and Canada (CAMH, University of Toronto). Dr. Squassina has gained extensive experience in genetic variations, gene expression analyses, cell cultures and data management and analysis. Dr. Squassina's research focuses on the investigation of the genetic underpinnings of bipolar disorder, schizophrenia, suicide and response to psychotropic medications. He has been principal investigator or co-investigator in a number of research international and local projects. Dr.

Squassina has published 32 papers in peer-reviewed journals, more than 20 abstracts and is member of the editorial team of several peer-reviewed journals.

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Athanassios Vozikis is Assistant Professor at the Department of Economics of the University of Piraeus. He holds a degree in Public Administration from the Panteion University, a M.Sc. in Health Informatics from National Kapodistriako University of Athens and a Ph.D. in Health Economics and Information Systems from the University of Piraeus. He has been a State Scholarships Foundation scholar for his M.Sc. and Ph.D. studies. He is member of the National Council of Public Health, member of various scientific associations and organizations and member of the editorial board and reviewer of several academic journals. He has participated in many research projects in the Health Care Sector, as well as in various other sectors. He has participated in as guest speaker in many Conferences and a number of his articles have been published in academic journals, academic issues and scientific conferences proceedings. He teaches Health Economics, Healthcare Management, Environmental Economics, Information Systems and Digital Economy courses at an undergraduate and postgraduate level. He has been Supervisor and referee of many dissertations and Ph.D. theses.

Bauke Ylstra

Professor

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In 1995 I graduated with work performed at the Departments of Genetics at the Free University in Amsterdam (NL) and the University of Vienna (A). Subsequently I performed a post-doc at the University of California in Berkeley (CA, USA) focusing on the identification of stable mRNA molecules on a genome-wide scale. In 1998 I accepted a position at the University of California at the Comprehensive Cancer Center (CA, USA) in San Francisco; Since, I have been specializing in cancer genomics. Currently, I am the coordinator of the Genome Core of the Cancer Center Amsterdam of the VU University Medical Center (VUMC-CCA, NL). My lab has been instrumental in the development and implementation of genome analysis laboratory and bioinformatics procedures for cancer research, with a focus on genome techniques for personalized medicine. In particular, we focus on methods for the detection of point mutations and chromosomal copy number analysis by next generation sequencing NGS. Our specialty is the analysis of DNA specimens of compromised quality, such as obtained from archival formalin fixed and paraffin embedded (FFPE) tumor specimens whose analysis is very important for studies of cancer.

Branka Zukic

Laboratory Head

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Branka Zukic (maiden Petrucev), was born in 1976, Republic of Serbia. She obtained her PhD in Molecular Biology from the University of Belgrade, Serbia in 2010. She works as Research Associate in the Laboratory for Molecular Biomedicine, Institute of Molecular Genetics and Genetic Engineering (IMGGE), University of Belgrade. Her research interests are studying the molecular mechanisms involved in the regulation of eukaryotic gene expression, analysis of molecular basis and diagnostic of various rare diseases, analysis of genetic variants important for optimization of drug therapy in the treatment of acute lymphoblastic leukemia. Her keen interest is in expanding the research toward pharmacogenetics and personalized medicine in health improvement. In particular, to assess the pharmacogenetic potential of promoter of human *TPMT* gene and its clinical relevance, to investigate influence of mercaptopurine drugs on *TPMT* gene promoter and genetic variants of variuos drug metabolizing enzyms, in order to improve the widely used mercaptopurine and methotrexate drugs therapeutic protocols. The long-term goal is to participate and support the implementation of pharmacogenomics and genome based medicine in public healthcare. She published 23 papers in peer-reviewed scientific journals. She has given several lectures in international conferences as invited speaker and actively participates in research projects received funding from national and international funding agencies. Branka gives lectures at PhD courses in Faculty of Biology, University of Belgrade. She is a member of Ethical Committee at IMGGE. From 2013, Branka Zukic is Head of the Laboratory for Molecular Biomedicine at IMGGE.

THE EMBO LECTURE

Douglas R. Higgs (EMBO Member)

Director, Weatherall Institute of Molecular Medicine

Director, MRC Molecular Haematology Unit, Weatherall Institute of

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Douglas Higgs (FRS, DSc, FRCP, FMedSci) qualified in Medicine 1974 and trained as a haematologist. He joined the MRC Molecular Haematology Unit (Oxford) in 1977 and is currently Professor of Haematology at the University of Oxford and Director of the Weatherall Institute of Molecular Medicine (WIMM). He has published 280 primary research articles including many in Nature, Science, Cell, Molecular Cell and Nature Genetics. His research has elucidated many of the principles underlying normal gene expression and the mechanisms by which this is perturbed in human genetic disease. He has received many prestigious international awards for his work and recently received the Royal Society Buchannan Medal for Medical Research.

The relationship between genome structure and function: Lessons from the globin loci

Douglas R. Higgs

University of Oxford, Institute of Molecular Medicine, MRC Molecular Haematology Unit, Oxford, UK

We have studied how transcriptional and epigenetic programmes are played out on chromatin spanning the terminal 500kb of human chromosome 16 (16p13.3) as hematopoietic cells undergo lineage fate decisions and differentiation. This region includes the alpha globin cluster and its regulatory elements, which are silenced via the Polycomb system in early progenitors, poised for expression in later progenitors and fully expressed during terminal erythroid differentiation. Other genes in this region are also up-regulated in an erythroid specific manner. Using a variety of approaches we have established the order in which silencing factors are removed, activating transcription factors bind and epigenetic modifications occur. In addition we have shown how chromosomal conformation and nuclear sub-localisation change during hematopoiesis. Natural *cis* and *trans* acting mutations (involving transcription factors and chromatin associated proteins) that cause alpha thalassaemia provide additional insight into how the long range regulatory elements may interact with the promoters of the globin genes, and other flanking genes, to activate their expression. Together these observations establish some of the general principles by which genes within their natural chromosomal environment are switched on and off during hematopoiesis. These findings add to our general understanding of the relationship between genome structure and function. Using principles derived from the globin cluster we are now asking, in more general terms, how genomic variation causes changes in gene expression. In particular, we are studying how changes in intergenic regulatory elements affect gene expression. This involves identifying significant changes in regulatory elements and linking these elements to the genes whose expression they control. Our ultimate aim is to unlock the vast amount of information derived from GWAS studies by understanding how common variation in regulatory elements may influence gene expression and ultimately contribute to human traits and predisposition to disease.

SCIENTIFIC PROGRAM

Day 1 - Thursday, 11 September 2014

08:00 – 14:30   Arrivals AND Delegates registration

SESSION 1 – Chairperson: G. Patrinos

14:30 – 14:45   Summer School coordinators
Introduction

14:45 – 15:15   *George P. Patrinos* (Patras, Greece)
Genomic Medicine in the global village

15:15 – 15:45   *Emmanouil Dermitzakis* (Geneva, Switzerland)
From population and personalized genomics to personalized medicine

15:45 – 16:15   **Coffee break**

16:15 – 17:30   **WORKSHOP 1 – RD-CONNECT**
A. Milan Macek (*Prague, Czech Republic*)
European genetics and rare disease initiatives
B. Ivo Gut (*Barcelona, Spain*)
RD-Connect: A database for rare disorders research
C. Olaf Riess (*Tubingen, Germany*)
**RD-Neuromics: -omics research for diagnosis and therapy in rare
neuromuscular and neurodegenerative diseases: An EU-funded FP7 project**

17:30 – 18:15   **POSTER SESSION 1 (PO.01-PO.07)**

18:15 – 19:30   **DAY ENDS – FREE TIME**

19:30 – 22:30   **Welcome reception**

Day 2 – Friday, 12 September 2014

08:00 – 09:30   **Breakfast**

09:30 – 11:00   **Abstract presentations1 – Chairperson: S. Pavlovic**

FT-01. *Vesna Spasovski* (Belgrade, Serbia)

The first extracellular loop of the PTCH1 protein: a true "hot spot" for *PTCH1* gene?

FT-02. *Irena Glumac* (Belgrade, Serbia)

High WT1 expression as a new molecular marker of poor prognosis in Serbian Acute Myeloid Leukemia patients with normal karyotype (AML-NK)

FT-03. *Danijela Drakulic* (Belgrade, Serbia)

Characterization of the 22q11.2 region in patients with clinical features of 22q11.2 deletion syndrome

FT-04. *Nataša Kovačević-Grujičić* (Belgrade, Serbia)

Antitumor effect of Meripilus giganteus Karst. methanolic extract via upregulation of *p53*, *BAX* and *SOX1* expression in HeLa cells

FT-05. *Danijela Stanisavljevic* (Belgrade, Serbia)

SOX14 expression during retinoic acid induced neural differentiation of pluripotent embryonal carcinoma stem cells

FT-06. *Adrijana Klajn* (Belgrade, Serbia)

SOX2 overexpression affects neural differentiation of human pluripotent NT2/D1 cells

FT-07. *Milena Milivojevic* (Belgrade, Serbia)

Functional characterisation of novel dominant-negative mutant of the human SOX18 protein

FT-08. *Biljana Stankovic* (Belgrade, Serbia)

Inflammatory bowel disease in Serbian population: association of proinflammatory gene variants with the disease and their combined contribution in the prediction of disease development

FT-09. *Natasa Tosic* (Belgrade, Serbia)

Molecular genetic markers as a base for administration of targeted therapy in acute promyocytic leukemia

SESSION 2 – Chairperson: B. Ylstra

11:00 – 11:30 *Alessio Squassina* (Cagliari, Italy)
Genomics and microarray technology

11:30 – 12:00 *Bauke Ylstra* (Amsterdam, the Netherlands)
Spatial copy number heterogeneity and relevance of chromosome 10q deletion in low-grade gliomas by whole genome sequencing

12:00 – 12:30 *Nduna Dzimiri* (Riyadh, Saudi Arabia)
The genetic intricacy of treating coronary artery disease

12:30 – 14:00 **Lunch break**

SESSION 3 – Chairperson: M. Dermitzakis

14:00 – 14:30 *Ming Ta Michael Lee* (Yokohama, Japan)
Pharmacogenomics and personalized medicine: From basic research to clinical application

14:30 – 15:00 *Ron H. van Schaik* (Rotterdam, the Netherlands)
Clinical pharmacogenomics and genomic medicine

15:00 – 15:30 *Vita Dolžan* (Ljubljana, Slovenia)
Clinical pharmacogenetic models for translation of pharmacogenetics to clinical practice

15:30 – 16:00 *Branka Zukic* (Belgrade, Serbia)
Pharmacogenomics of 6'mercaptopurin treatment in childhood acute lymphoblastic leukemia

16:00 – 16:30 **Coffee break**

SESSION 4 – Chairperson: E. Vayena

16:30 – 17:00   *Effy Vayena* (Zurich, Switzerland)
Personal Genomics: Clinical and personal utility at an ethical crossroad

17:00 – 17:30   *Sotiria Kechagia* (Geneva, Switzerland)
Direct-to-Consumer genetic and pharmacogenomic testing: A legal perspective

17:30 – 18:15   **POSTER SESSION 2 (PO.08-PO.14)**

18:15 – 19:30   **DAY ENDS – FREE TIME**

19:30 – 21:00   **Dinner**

Day 3 - Saturday, 13 September 2014

08:00 – 09:30 **Breakfast**

09:30 – 11:00   **Abstract presentations 2 – Chairperson: P. Danielson**

FT-10. *Philip Danielson* (Denver, CO, USA)

   Application of Mass Spectrometry in Forensic Serology

FT-11. *Magdalena Stepien* (Zurich, Switzerland)

   A physician's perspective on direct-to-consumer genetic testing

FT-12. *Agata Maciejak* (Warsaw, Poland)

   Identification of a peripheral blood transcriptional biomarker panel associated with post–myocardial infarction heart failure

FT-13. *Aldesia Provenzano* (Florence, Italy)

   Heterogeneous Genetic Alterations in Sporadic Nephrotic Syndrome Associate with Resistance to Immunosuppression

FT-14. *Sabrina Giglio* (Florence, Italy)

   Therapeutic implications of novel mutations of RFX6 gene associated with early-onset diabetes

FT-15. *Jihène Bouassida* (Tunis, Tunisia)

   Screening of *CYP1B1* gene in Tunisian patients with Primary Congenital Glaucoma

FT-16. *Konstantina Chalikiopoulou* (Patras, Greece)

   Pharmaco-epigenomic analysis of *MAP3K5* gene promoter in β-type hemoglobinopathies patients under hydroxyurea treatment

FT-17. *Vasiliki Chondrou* (Patras, Greece)

   Differential molecular profiling of human hematopoietic tissues during human ontogenesis - A hemoglobinopathies therapeutics approach

FT-18. *Eleni Dalabira* (Patras, Greece)

   Pharmacogenomics in Europe: Applications in public health

SESSION 5 – Chairperson: A. Squassina

11:00 – 11:30   *Clint Mizzi* (Msida, Malta)

Whole genome sequencing and data interpretation in genomic medicine

11:30 – 12:00 *George Potamias* (Heraklion, Greece)

Boosting pharmacogenomics: A translational bioinformatics perspective

12:00 – 12:30 *George P. Patrinos* (Patras, Greece)

Databases in genomics

12:30 – 14:00 **Lunch break**

SESSION 6 – Chairperson: G. Potamias

14:00 – 14:45 **CORPORATE LECTURE – CERGENTIS**

Max van Min (Utrecht, the Netherlands)

Targeted locus amplification

14:45 – 15:15 *Judit Kumuthini* (Cape Town, South Africa)

Sustainable capacity development in personalized medicine

15:15 – 15:45 *Athanassios Vozikis* (Piraeus, Greece)

The intersection of genomics and health economics

15:45 – 16:15 **Coffee break (sponsored by eMoDiA)**

16:15 – 17:30 **WORKSHOP 2 – eMoDiA**

A. *Theodora Katsila* (Patras, Greece)

Pharmacogenomics initiatives: eMoDiA

B. *George Potamias* (Heraklion, Greece)

Towards an electronic PharmacoGenomics Assistant (ePGA)

C. *Evgenia Kartsaki* (Heraklion, Greece)

Pharmacogenomic Translation Services

D. *Kleanthi Lakiotaki* (Heraklion, Greece)

A Pharmacogenomics Dashboard of 1000 Genomes Project

17:30 – 19:30 **DAY ENDS – FREE TIME**

19:30 – 21:00 **Dinner (sponsored by eMoDiA)**

Day 4 – Sunday, 14 September 2014

08:00 – 09:00 **Breakfast**

09:00 – 12:00 **Visit at the AFEA archaeological site and museum**

12:30 – 14:00 **Lunch break at Aghia Marina**

SESSION 7 – Chairperson: M. Ferrari

14:00 – 14:30 *Maurizio Ferrari* (Milan, Italy)
How to improve molecular diagnostic literacy in developing countries

14:30 – 15:00 *George P. Patrinos* (Patras, Greece)
Public Health Genomics: From concept to reality

15:30 – 16:00 **Coffee break**

16:00 – 17:30 **Abstract presentations 3 – Chairperson: T. Katsila**

FT-19. *Cristiana Pavlidis* (Patras, Greece)
   **Whole genome sequencing analysis of a Greek family affected by
   Adamantiades-Behcet disease**

FT-20. *Eleni Merkouri-Papadima* (Patras, Greece)
   **Identification of genomic variants leading to Amyotrophic Lateral Sclerosis
   Causes in Greek population using a whole genome sequencing approach**

FT-21. *Katja Goričar* (Ljubljana, Slovenia)
   **Clinical-pharmacogenetic model for prediction of treatment outcome in
   malignant mesothelioma**

FT-22. *Barbara Jenko* (Ljubljana, Slovenia)
   **The pharmacogenetic model of influence of transporters polymorphisms
   and clinical factors on methotrexate inefficacy in rheumatoid arthritis
   patients**

FT-23. *Maria Manica-Cattani* (Santa Maria, Brazil)

Guaraná and its main bioactive molecules modulates differentially the *D. melanogaster* transcriptome

FT-24. *Kleanthi Lakiotaki* (Heraklion, Greece)

Towards a pharmacogenomics information system for personalized medicine

FT-25. *Evangelia-Eirini Tsermpini* (Patras, Greece)

Role of the rs6313 and rs1799978 variants as pharmacogenomic biomarkers in Greek, Italian and Croatian schizophrenia patients

FT-26. *Konstantinos Siatis* (Patras, Greece)

Development of a novel tumor homing compound targeting selectively glioblastoma cells

FT-27. *Zoi Zagoriti* (Patras, Greece)

Assessment of the *STAT4* rs7574865 SNP in genetic susceptibility of early-onset Myasthenia gravis

17:30 – 18:15   **POSTER SESSION 3 (PO.15-PO.21)**

18:15 – 19:30   **DAY ENDS – FREE TIME**

19:30 – 22:00   **Farewell Dinner – Traditional Party**

Day 5 – Monday 15 September 2014

08:00 – 09:30 **Breakfast**

09:30 – 10:45 **Career development session**
Vita Dolžan (Ljubljana, SI; <u>Chairperson</u>)
Sonja Pavlovic (Belgrade, RS)
Emmanouil Dermitzakis (Geneva, CH)
Judit Kumuthini (Cape Town, ZA)
A. Nazli Basak (Istanbul, TR)
Philip Danielson (Denver, CO, USA)
Nduna Dzimiri (Riyadh, SA)

THE EMBO LECTURE – Chairperson: G. Patrinos

10:50 – 11:00 Introduction
11:00 – 11:45 *Douglas R. Higgs* (<u>EMBO Member</u>, Oxford, UK)
Switching genes on and off during differentiation and development

BEST ABSTRACT SESSION – Chairperson: G. Patrinos

11:45 – 12:00 **Best Abstract 1 –** <u>*M Bartsakoulia*</u>*, V Boczonadi, A Gomez-Duran, P Yu W Man, P F Chinnery, R Horvath (*Newcastle, UK)
Studying the effect of L-cysteine in MELAS and MERRF

12:00 – 12:15 **Best Abstract 2 –** <u>*S Pavlovic*</u>*, B Stanic, J Kostic, N Pejanovic, B Lucic, N Tosic, I Glumac, D Janic, L Dokmanovic, S Jankovic, N Suvajdzic Vukovic, D Tomin, B Mihaljevic, M Todorovic, J Jelicic, D Krstajic, M Popovic, I Bogicevic, M Stojiljkovic* (Belgrade, Serbia)
Next-generation sequencing analysis of hematological malignancies: Serbian experience

12:15 – 12:30 Summer School coordinators
Conclusions

12:30 Delegates departure

PLENARY LECTURES,
WORKSHOPS
&
CORPORATE LECTURE

PLENARY LECTURES

PL-01. Genomic medicine in the global village

G P Patrinos
University of Patras, School of Health Sciences, Department of Pharmacy, Patras, Greece

Medicine prioritization is a high stakes undertaking for developing countries and pharmacogenomics promises to materialize personalized treatment. Many developing countries currently lack the knowledge and/or the resources to individualize drug therapy. Here, we propose a multi-step approach for the implementation of pharmacogenomics in developing countries, focusing on emerging European countries. This approach includes (a) Collection of DNA samples from healthy volunteers to determine the various pharmacogenomic markers allele frequencies in this population, using a 2-tiered approach (b) Conduct a comprehensive health economic analysis to illustrate the cost-effectiveness of pharmacogenomic testing, (c) Survey the level of awareness and education of several stakeholders over genetics, including genetic laboratories, pharmacists, the general public and healthcare professionals, (d) Organization of education activities to disseminate pharmacogenomics knowledge to society, and (e) Establishment of national guidelines for medication prioritization. Since 2009, this approach is being implemented in over 20 European countries, which includes genotyping of over 1,000 DNA samples to determine the allele frequencies in 1,936 pharmacogenomic markers in 220 pharmacogenes, using the DMET+ microarray (Affymetrix, Santa Clara, CA, USA). We identified over 300 pharmacogenomic markers that display divert allele frequencies compared to those of the Caucasian population ($p<0.05$), that are currently being replicated in a larger multiethnic population sample. We are also concluding a cost-benefit analysis to demonstrate the usefulness of integrating pharmacogenomics in everyday clinical decision-making process, to adjust the acenocoumarol-dosing scheme, while since 2009 we have initiated a pharmacogenomics educational meeting series for healthcare professionals and regulators in Greece and elsewhere abroad (the Golden Helix Pharmacogenomics Days). This approach could expedite integration of pharmacogenomics in healthcare decision-making process, provide guidelines for medication prioritization for individual countries, using pharmacogenomic information and lead to the development of local infrastructure for future pharmacogenomic research studies. Ultimately, whole genome sequencing could be implemented to obtain personalized pharmacogenomics profiles. We analyzed whole genome sequences of 482 unrelated individuals of various ethnic backgrounds and identified approximately 482000 variants in 231 ADMET-related genes, a large number of which were novel and likely functional. This finding underlines the potential of whole genome sequencing to capture several novel and potentially important ADMET gene-related variants in individual patients and demonstrate that whole genome sequencing, unlike conventional genetic screening methods, is necessary to accurately determine an individual's personalized pharmacogenomics profile, which would expedite bringing personalized medicine closer to reality.

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PL-02. From population and personalized genomics to personalized medicine

E Dermitzakis

University of Geneva Department of Genetic Medicine, Geneva, Switzerland; Biomedical Research Foundation of the Academy of Athens, Greece

Molecular phenotypes are important phenotypes that inform about genetic and environmental effects on cellular state. The elucidation of the genetics of gene expression and other cellular phenotypes are highly informative of the impact of genetic variants in the cell and the subsequent consequences in the organism. In this talk I will discuss recent advances in key areas of the analysis of the genomics of gene expression and cellular phenotypes in human populations and multiple tissues and how this assists in the interpretation of regulatory networks and human disease variants. I will also discuss how the recent advances in next generation sequencing and functional genomics are informing us about the impact of regulatory variation in cancer. Finally, I will present some perspectives on how these developments are bringing us closer to the promise of personalized medicine.

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PL-03. Genomics and microarray technology

A Squassina

University of Cagliari, Department of Biomedical Sciences, Section of Neurosciences and Clinical Pharmacology, Cagliari, Italy

Genetic research have significantly benefitted from the advent of high-throughput technologies. Giving the possibility to explore the whole genome with a large number of molecular variants at the same time, 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 pharmacology. 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), measure the expression of genes and different populations of non-coding RNAs as well as proteins. While next-generation sequencing is becoming more precise and affordable, 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 different microarrays available on the market, pointing to their advantages and strengths and discussing pitfalls and weaknesses, with a particular focus on examples of their utility in human diseases and in pharmacogenomics.

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PL-04. Spatial copy number heterogeneity and relevance of chromosome 10q deletion in low-grade gliomas by whole genome sequencing

I Scheinin, H F van Thuijl, D Sie, H F van Essen, P P Eijk, F Rustenburg, A Alentorn, G A Meijer, A Idbaih, M A van der Wiel, H Bengtsson, A B Olshen, J J Heimans, E Aronica, J C Reijneveld, P Wesseling, D Pinkel, D G Albertson, **B Ylstra**.

VU University Medical Center,
Amsterdam, the Netherlands

Introduction: The disease course of patients with diffuse low-grade gliomas (LGGs) is notoriously unpredictable. Detailed analysis of the genetic make-up is therefore key to understand this wide variety in overall survival of patients diagnosed with LGGs. Reports on the prognostic value of CNAs other than 1p/19q co-deletion are conflicting, which may be explained by spatial copy number heterogeneity.

Aim: Prognostic implications of spatial and temporal copy number aberrations in LGGs by whole genome sequencing.

Methods: Approximately 25% of LGG patients have a life expectation of more than 20 years following diagnosis, which necessitates collection of samples with long clinical follow up information. Therefore archival material was selected for this project and WGS was developed to access these samples without the requirement for a normal reference. We collected 156 formalin-fixed and paraffin-embedded (FFPE) samples in a discovery cohort of 98 LGG patients with extensive clinical follow-up data, which included recurrent tumours and spatially distinct regions. An independent cohort of 126 samples was obtained from a recently published study (Alentorn et al, Neuro-oncology 2014). Technical challenges for genome-wide inference of copy number aberrations include repetitive and common DNA sequences in the genome and sequence variation across the general population, as well as the compromised and variable quality of DNA obtained from archived tissue samples. We developed a robust and cost effective method that infers copy number aberrations from WGS data with approximately 0.1x coverage, without the need for a reference signal. This method implements (1) a combined LOESS correction for mappability and high guanine and cytosine nucleotide content, and improves on previous methods by (2) comprehensive filtering based on public genome project data, 1000 Genomes project and ENCODE blacklists.

Results: Both prognostic value, temporal evolution and spatial heterogeneity of CNA were assessed by WGS. We confirmed prognostic favourable value of 1p/19q co-deletion, and demonstrated loss of 10q to be an unfavourable marker. In paired recurrences 10q loss was invariably maintained and surfaced in 4 additional recurrences of the discovery cohort. In spatial regions of LGGs we recognized extensive copy number heterogeneity; 15 of 17 LGGs show spatial variability of CNAs. 1p/19q co-deletion is homogeneous, while loss of 10q is heterogeneously present.

Conclusions: We present clinically relevant CNAs, but also demonstrate extensive spatial copy number heterogeneity in diffuse LGGs that might complicate unequivocal biomarker discovery.

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PL-05. The genetic intricacy of treating coronary artery disease

N Dzimiri

Genetics Department, King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia

The circulatory function is regulated by various signaling pathways controlling cardiac contractility, vascular activity and volume output. Hence, a change in any one of these systems is likely to influence the function of those controlling other circulatory components. Not surprisingly therefore, cardiovascular disease pathways are often a manifestation of interactions of regulatory components of various disease

traits, such as hypertension, type 2 diabetes and dyslipidaemia, among themselves, as well as with environmental factors. These diseases underlie, to large extent, genetic changes, which renders the drug therapy of maladies, such as coronary heart disease difficult, as it entails possible involvement of disease pathways of multiple cardiovascular risk traits. This is further complicated by the fact that individuals do not always respond to drug therapy in the same fashion, partly due to variations in their genetic constitutions, compounded by the fact that these variations may also differ among ethnical populations. Naturally, this scenario in turn renders it crucial to decipher these genetic differences, not only among individuals but also between ethnical groups, as a prerequisite for achieving optimal therapeutic outcomes. However, while great strides have been accomplished in this direction in recent years, much more remains to be learnt in order to realize the ultimate goal of providing the most suitable individual therapy for these complex diseases.

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PL-06. Pharmacogenetics and Personalized Medicine: from basic research to clinical application

M Lee

Laboratory for International Alliance on Genomic Medicine, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan

Numerous genetic markers have been identified to associated drug induced adverse reactions and this has prompted the US to include genetic information in drug label for more than 10 drugs. However, the use of pharmacogenetics in clinical practice has been limited mostly due to lack of understanding and experience with the use of pharmacogenetics by the physicians and the limited access to genotyping facilities. Carbamazepine (CBZ) is the main drug causing Stevens-Johnson syndrome (SJS) and its related disease, toxic epidermal necrolysis (TEN), in Southeast Asian countries. HLA B*1502 has been shown to strongly associated CBZ-induced SJS/TEN. A study was then conducted to determine whether CBZ-induced SJS/TEN can be prevented by identifying individuals at risk using HLA-B*1502 genotyping and evaluating the effectiveness of prospective HLA-B*1502 screening. Patients who had not previously received CBZ, with indications for CBZ, underwent prospective HLA-B*1502 screening. CBZ was withheld from patients testing positive for HLA-B*1502. All patients were followed by telephone interview once a week for two months to monitor symptoms of adverse drug reactions. Between July 2007 and April 2010, 4877 subjects were recruited from 23 hospitals in Taiwan. The HLA-B*1502-positive patients (7.7% of the total) were given alternative medication. The remaining 92.3% of patients (HLA-B*1502-negative) were started on CBZ. Of all the enrolled patients, 4.3% developed mild, transient skin rashes while 0.1% had more wide-spread rashes and were hospitalized. None of the CBZ-treated HLA-B*1502-negative patients developed SJS/TEN, contrasting with the estimated 10 cases of CBZ-SJS/TEN in the historical control (0.23% of CBZ users) (p value=0.00016). I will also present our recent discovery which we identified SNPs strongly associated with lithium treatment response. The implementation of pharmacogenetics in clinical use will also be discussed.

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PL-07. Clinical pharmaco-genomics and genomic medicine

R H N van Schaik

Department of Clinical Chemistry, Erasmus University Medical Hospital, Rotterdam, the Netherlands

Interindividual variation in drug metabolism is a complicating factor affecting successful drug therapy. Although observed and accepted for a long time, and being responsible for 5-7% of hospitalizations each year, we are currently in a position to improve drug therapy based on the genetic background of each patient. With the knowledge on the existence and the subsequent effects of single nucleotide polymorphisms in the genes of drug metabolizing enzymes and drug transporters affecting systemic drug exposure, and tools available to detect these at reasonable costs, we are entering the era of Genomic Medicine. Although over 5,000 articles per year are currently being published on genomic markers to guide drug therapy, clinical implementation is still slow. Yet, progression is being made. Several tests have been accepted by the clinic, whereas others have not. And, surprisingly, this acceptance deviates not only from country to country, but also from clinic to clinic.
Our own experience in how to implement and use pharmacogenetics in clinical diagnostics will be illustrated, based on our 10 year experience. This implementation strategy covers education, availability of testing, laboratory and clinical guidelines, quality, feedback from clinicians and patients, reporting, financial and ethical aspects, networking and interlaboratory competition.

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PL-08. Clinical pharmacogenetic models for translation of pharmacogenetics to clinical practice

V Dolžan

University of Ljubljana, Faculty of Medicine, Institute of Biochemistry, Pharmacogenetics Laboratory, Ljubljana, Slovenia

It is anticipated that the advances of genomic medicine will support a shift from the era of empirical population-based treatment approaches to an era of preventive, personalized, predicitive and participatory health care. Translational research in the field of personalized medicine investigates biomarkers that could help customize treatment for individual patients, thus leading to more effective treatment with fewer adverse events. Pharmacogenetic studies are often focused on functional single nucleotide polymorphisms in genes coding for drug metabolizing enzymes, drug transporters or drug targets, but it is becoming clear that in most cases more than one gene is implicated in drug response and that patient's clinical characteristics and environmental factors may interact with genetic factors and have to be taken into account when predicting treatment outcomes. Furthermore pharmacogenetic studies are often limited to detection of associations between genetic variability and treatment outcomes and their results are seldom incorporated in actionable forms such as scores or dosing guidelines. All this makes translation of pharmacogenetic results into clinical practice very challenging. Pharmacogenetic models including both clinical and genetic parameters could be a useful tool that would help guide treatment selection, however only a few pharmacogenetic models have been

published to date and most of them have not been translated into clinical practice. Two examples of clinical-pharmacogenetic models developed in our laboratory will be presented to demonstrate how such models could facilitate the stratification of patient population based on predicted drug response for selection of the most favorable treatment based on the clinical and genetic characteristics of an individual patient.

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PL-09. Pharmacogenomics of 6-mercaptopurin treatment in childhood acute lymphoblastic leukemia

B Zukic

Institute of Molecular Genetics and Genetic Engineering University of Belgrade, Serbia

Childhood acute lymphoblastic leukemia (ALL) represents one of the best examples of progress in disease treatment based upon the incorporation of the principles of pharmacogenomics. Administering of mercaptopurine (6-MP) in patients with variants in the genes involved in the drug metabolism leads to severe hematotoxicity. We have investigated genetic variants of *TPMT*, *ITPA*, *MDR1* and ABCC*4* genes, relevant for metabolism of 6-MP in 150 Serbian childhood ALL using PCR and sequencing methodology. *TPMT* gene expression and 6-MP toxicity *in vitro* and *in vivo* was analysed using functional CAT and Real-Time PCR assays. Genetic variants in TPMT exons were found in 7.5% of patients. The therapy for pediatric ALL patients with these genetic markers was modified, which contributed to the efficiency of treatment. Administering reduced 6-MP dosages in the initial phase of maintenance, allowed *TPMT*-deficient and heterozygous patients to later receive full protocol doses of 6-MP. We also investigated the influence of 6-MP on *TPMT* gene expression. Functional assays *in vitro* showed that *TPMT* promoter activity depended on the architecture of VNTRs in the promoter. Study of *TPMT* gene expression in childhood ALL patients before and after administering 6-MP therapy, revealed that 6-MP has a positive effect on transcription of *TPMT* gene, with the median increase of 280%. Analysis of variants in *ITPA*, *MDR1* and ABCC4 genes indicates their pharmacogenomics potential. VNTR region of *TPMT* gene promoter is new candidate pharmacogenomic marker. The transcription of *TPMT* gene is positively influenced by 6-MP therapy. Patients are more susceptible to 6-MP induced toxicity in the early stages of the therapy. Therefore, for *TPMT*-genetic variant carriers, administering of reduced 6-MP dosages in the initial phase of maintenance is recommended. Later, these patients are allowed to receive full protocol doses of 6-MP. Application of pharmacogenomic principles has improved the outcome for children with ALL.

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PL-10. Personal Genomics: Clinical and personal utility at an ethical crossroad

E Vayena

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Direct-to-consumer (DTC) genetic services have generated enormous controversy from their first emergence. A dramatic recent manifestation of this is the FDA's cease and desist order against 23andMe, the leading

provider in the market. Critics have argued for the restrictive regulation of such services, and even their prohibition, on the grounds of the harm they pose to consumers. Their advocates, by contrast, defend them as a means of enhancing the autonomy of those same consumers. The debate has focused on the limited clinical utility of such tests while emerging literature suggests that other utilities including personal utility maybe at stake and need to be considered. I will present results from a study of attitudes towards DTC genetics and the role of "research participation" as a motive for interest in genetic testing. I will discuss the lessons that we should learn from the recent debates on DTC genetics and suggest some approaches for the way forward.

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PL-11. Personal genomics in Greece: An overview of available direct-to-consumer genomic services and the relevant legal framework

S Kechagia

Department of Genetic Medicine and Development, School of Medicine, University of Geneva, Geneva, Switzerland

The aim of this study is to provide an overview of the DTC genomic services available in Greece and the legal framework within which they operate. Based on literature review, a questionnaire that was distributed in a genetics conference in Greece and in-depth interviews with human geneticists in Greece we assess the landscape of the DTC genomic testing market and highlight possible particularities of Greek consumers.

Furthermore we identify the existing legal framework regarding DTC genetic testing. Our interest is not limited only to issues such as consumer protection laws, lab quality accreditation and the provision of genetic counseling.

We also explore the role of medical specialties and their respective legal responsibilities in the Greek context, since for example the specialty of Clinical Geneticist does not exist. We also explore the legal authority of the National Organization of Medicines (E.O.F.) regarding the approval of genetic tests and specific issues relating to paternity tests. We identify gaps in the current regulatory scheme and conclude with recommendations for a more comprehensive legal framework.

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PL-12. Boosting pharmacogenomics: A translational bioinformatics perspective

G Potamias

Foundation of Research and Technology Hellas, Institute of Computer Science, Biomedical Informatics laboratory, Heraklion, Crete, Greece

In the post-genomic era, the rapid evolution of high-throughput genotyping technologies and the increased pace of production of genetic research data, are continually prompting the development of appropriate informatics tools, systems and databases as we attempt to cope with the flood of incoming genetic information. Alongside new technologies that serve to

enhance data connectivity, emerging information systems should contribute to the creation of a powerful knowledge environment for genotype-to-phenotype information in the context of translational medicine. In the area of pharmacogenomics (PGx) and personalized medicine, it has become evident that data and knowledge base applications providing important information on the occurrence and consequences of gene-variants involved in pharmacokinetics, pharmacodynamics, drug efficacy and drug toxicity, will become an integral tool for researchers and medical practitioners alike. At the same time, two fundamental issues are inextricably linked to current developments, namely data sharing and data protection. Here, we discuss on highthroughput and next generation sequencing technology and its impact on pharmacogenomics research. In addition, we present advances and challenges in the field of pharmacogenomics information systems which in turn triggered the development of an integrated electronic 'pharmacogenomics assistant'. The system is designed to provide personalized drug recommendations based on linked genotype-to-phenotype pharmacogenomics data, as well as to support biomedical researchers in the identification of pharmacogenomic related gene variants. The provisioned services are tuned in the framework of a single-access pharmacogenomics portal.

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PL-13. Next-generation sequencing and data interpretation in genomic medicine

C Mizzi

University of Malta, Department of Physiology and Biochemistry
Faculty of Medicine and Surgery, Msida, Malta

The development of Next Generation Sequencing created a new paradigm for analysing biomedical data by achieving efficient and reliable whole genome sequencing, targeted and exome sequencing and transcriptomics (RNA-Seq). Next Generation Sequencing can be used in genomic medicine by studying populations, families or individual sequencing requiring diverse pipelines for data interpretation.

With current technologies, sequencing a large number of samples, for population studies is both time-consuming and expensive thus sequencing of a pool of DNA is sometimes considered as a solution. Sequencing targeted locations for example specific genes have been used in the field of genomic medicine. Next Generation Sequencing made it possible to study the whole genomes of families with inheritable disorders or unrelated individuals.

Interpreting different Next Generation Sequencing data requires two steps. Results from a Next Generation Sequencer need to be assembled to a reference genome and the variants called. The second challenge is to extract information from a the variants to find those few variants which are disease causing or relevant to our analysis. This presentation will show how different approaches of analysing huge data sets can be successful for genomic medicine.

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PL-14. Databases in genomics: The National Genetic database paradigm

G P Patrinos

University of Patras, School of Health Sciences, Department of Pharmacy, Patras, Greece

Recent progress in disease genetics and genome-related medicine has been dramatic, with enormous amounts of data now being generated in a multitude of laboratories and medical centers. However, this progress has not been matched by adequate database projects that can gather and organize these data to enable their useful exploitation. The domain is complex, entailing core databases, locus-specific databases, national mutation databases, genotype-phenotype databases and patient databases – and much work needs to be done to properly develop and integrate these various resources. Many factors contribute to this state of affairs (e.g., technological hurdles, publication requirements), but a lack of targeted funding is arguably the most fundamental problem. Here the state of the art of National genetic databases will be presented. These resources are structured and continuously updated data repositories recording the various spectra of causative genomic variations for any gene or disease in different populations and ethnic groups worldwide. The data content of these resources can be exploited mainly to study gene/mutation flow and admixture patterns, human demographic history and possibly to stratify national molecular diagnostic services and can be nicely complement the data content of either central (or core) and/or locus-specific databases (LSDBs). FINDbase (Frequency of INherited Disorders database; http://www.findbase.org), is a worldwide database pertaining to frequencies of causative mutations, leading to inherited disorders in various populations and ethnic groups worldwide. This resource contains data only in an aggregated manner, *i.e.*, allele frequencies without any sensitive personal data of their carriers, in order to maintain anonymity. All published data entries are recorded against their corresponding unique PubMed ID, whereas in case of unpublished information (e.g. personal communication or aggregated LSDB datasets), the microattribution approach is being used, using the contributor's unique ResearcherID, an approach that not only provides incentives to potential data contributors to share their data with the broader scientific community but also allows unambiguous identification of curated data when data update or correction is needed. The entire FINDbase data content is subdivided into 3 modules, namely causative mutations allele frequencies, pharmacogenomics markers allele frequencies and genetic disease summaries and is based on the established recommendations and guidelines to develop nation-wide projects to document the genetic heterogeneity in various countries. Based on this concept, over 90 National Genetic databases have been developed, using the next generation of the *ETHNOS* software that is based on data warehousing. We anticipate that these resources would pave the path to whole genome data repositories for distinct populations in an effort to precisely document not only the variable incidence of rare genetic disorders and the corresponding mutation spectrum but also the "genography" of various populations around the globe.

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PL-15. Sustainable capacity development in personalized medicine

J Kumuthini, E Chimusa, I van Jaarsveld, R Hiller

Centre for Proteomic and Genomic Research (CPGR), University Of Cape Town (UCT), Observatory, Cape Town, South Africa

The multidisciplinary nature of the bioinformatics field, coupled with rare and depleted expertise, is a critical problem in the advancement of bioinformatics in Africa. Further impediments include limited internet connectivity, lack of computational resources and sub-standard research facilities. Individuals who receive international training in highly resourced environments usually struggle to function or implement their expertise and knowledge when they return to their resource-stricken native environments. Short-term training programs have proved to be unsustainable and costly since knowledge and skills are not retained over time and limit the impact of such training. The KTP is a research and education model conceptualized to address these problems in a sustainable manner to stimulate, enhance and strengthen African bioinformatics capacity especially in the field of personalized medicine and pharmacogenomics. Its aim is to cost effectively facilitate the transfer of knowledge and skills from experienced, internationally recognised experts to local scientists. The CPGR, with its partner institutions of KTP as hosts, facilitate the match making process by identifying experts, training requirements and potential research associates. Instead of several associates travelling to well established labs for short periods of time, experts are brought in to interact and conduct high-quality research agendas locally. Experts and associates are brought together to work on relevant projects through which transfer of knowledge and skills is achieved naturally. The advantage of the approach is that several associates benefit from one expert with potential for themselves to become a trainer, while minimizing travel and accommodation expenditure. The programme is assessed by project outputs such as number and quality of publications, conference participation, patents, genomics data, or intellectual properties secured and the number of successfully trained associates and number of experts available in the expert base.

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PL-16. How to improve molecular diagnostic literacy in developing countries

M Ferrari

University Vita-Salute San Raffaele Division of Genetics and Cell Biology, San Raffaele Scientific Institute, Milan, Italy

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PL-17. Public Health Genomics: From concept to reality

G P Patrinos

University of Patras, School of Health Sciences, Department of Pharmacy, Patras, Greece

In the post-genomic era, genomics has gradually begun to assume a central role in modern medical practice. Public Health Genomics plays a central role in facilitating the smooth adopton of genomics into mainstream clinical practice. According to the Bellagio Statement (2005: GRAPH*Int*, PHGEN, IPHG), "Public Health Genomics (PHG) is the responsible and effective translation of genome-based knowledge and technologies into public policy and

health services for the benefit of population health." Public Health Genomics consist of various disciplines, including but not imited to increasing general public awareness, enhancing healthcare professionals genomics education, addressing the various ethical legal and social lissues pertaining to the implementation of genomics in medicine, fine mapping of the opinions of the various stakeholders and policy makers theat could play a role in genomics integration to healthcare decision making, and so on. The harmonization of Public Health Genomics practices in various countries is an even more challenging task.

In several countries in Europe, very little is currently known regarding the level of awareness of healthcare professionals with respect to pharmacogenomics and personalized medicine. A nationwide survey of the views of a total of 1,717 individuals from the general public, and of 496 medical practitioners with regard to genetic testing services in Greece indicated that a large proportion of the general public is aware of the nature of DNA, genetic disorders and the potential benefits of genetic testing, although this proportion declines steadily with age, while a large proportion of the interviewed sample would be willing to undergo genetic testing even if the costs of analysis were not covered by healthcare insurance. However, a relatively small proportion of the general public has actually been advised to undergo genetic testing, either by relatives or physicians. Most physicians believe that the regulatory and legal framework that governs genetic testing services in Greece is rather weak. Interestingly, the vast majority of the general public strongly opposes direct-access genetic testing, and most would prefer referral to be from a physician rather than from a pharmacist.

In a follow up study of the opinions of 86 pharmacists and 208 physicians, with a view to assessing their level of awareness of pharmacogenomics and personalized medicine we showed that around 60% of pharmacists consider their level of knowledge of personalized medicine to be very low, with around 80% of pharmacists and 58% of physicians intimating that they would be unable to provide sufficient information or explain the results of pharmacogenomic tests to their customers or patients, respectively. This situation may be directly related to the low level of their undergraduate education in genetics and pharmacogenomics, as confirmed by an assessment of the pharmacists' knowledge of basic genetics/genomics. Further, our surveys revealed that physicians are more often involved with personalized medicine and pharmacogenomics in their routine practice than pharmacists, and have more frequently advised their patients to undergo genetic and/or pharmacogenomic testing. Interestingly, only 7% of the pharmacists provide sample collection kits for downstream genetic analysis over the counter, a much larger proportion, although 30% claim to be in favor of direct-to-consumer genetic testing in principle. Similar results were also found in a recent study in a group of 200 medical professionals and students from the University of Cagliari (Italy).

In a related study, we used the computerized version of the *PolicyMaker* political mapping tool to collect and organize important information about the pharmacogenomics and genomic medicine policy environment, to assess the policy's content, the major players, their power and policy positions, their interests and networks and coalitions that interconnect them in Greece. Our findings indicate that the genomic medicine policy environment in Greece seems to be rather positive, as the vast majority of the stakeholders express their medium to high support in the initially set goals of genomic medicine

policy environment. The Ministry of Health and public healthcare insurance funds seems to oppose, most likely due to financial constrains.

Overall, our findings constitute the basis for an improved assessment of the views of the various stakeholders in relation to personalized medicine in Greece. It is to be hoped that these studies will not only improve, but also expedite, the integration of genomics into the medical decision-making process in Greece but will also set the stage for replicating these surveys in other European countries and to contribute in selecting and implementing policy measures that will expedite the adoption of genomics into conventional medical interventions. Lastly, it must be argued that scientists have a professional responsibility to effectively communicate current knowledge and views about potential applications to the public in order to better address and resolve genomics illeteracy issues.

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PL-18. The intersection of genomics and health economics

A Vozikis

University of Piraeus, Economics Department, Piraeus, Greece

A basic tenet of economics is that people make decisions to improve their well-being. For most commodities, price is a measure of perceived improvements in well-being, or value, and people make decisions on the basis of value. These principles, however, often do not apply in health care. Health care economics tries to gain a better understanding of the value of one health care intervention compared to

an alternative approach, taking into consideration all the impacts across patients, providers, and the health care system. This value can be measured in terms of price, improvements in quality of life, a longer life expectancy, resources saved, health state, and so on. Health Economists use several different tools to carry out economic evaluations of health care interventions, including cost-minimization analysis, cost-benefit analysis, cost-effectiveness analysis (CEA), and cost-utility analysis (CUA). The gold standard in the field has become CUA because it typically measures outcomes through a metric called a quality-adjusted life year (QALY) and allows for comparisons across interventions. Another standard measure in health economics is the incremental cost-effectiveness ratio, which is defined as the difference in cost between two interventions divided by the difference in their effectiveness. This metric can fall into four different quadrants on what is called a cost-effectiveness plane. Whether genome sequencing is cost-effective depends on the outcome that is being measured. These outcomes could be measured in terms of base pairs sequenced per dollar, the number of clinically meaningful genetic variants identified, diagnoses received, clinical actions taken, or patient outcomes. Many factors could influence cost-effectiveness in pharmacogenomic testing. Important factors include the prevalence and penetrance of the genetic variant, the cost and accuracy of the test, the prevalence of the disease and the outcomes if left untreated, and the effectiveness and cost of treatments.

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WORKSHOPS

WS-01 European genetics and rare disease initiatives

M Macek Jr.

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European Union Member State policies and actions in the field of rare disease (RD), which comprise majority of genetic diseases listed in OMIM, are rapidly evolving. Currently several countries have taken action to adapt their health care system to meet the needs of the RD patient community, or plan to do so. With regard to centres of expertise (CE), there are three categories of countries: 1) those which have a policy regarding RD and have CE within this framework (DK, FR, IT, NO and SE); 2) those which have established CE, though not specifically for RD (BE, HR, CR, SF, GR, IRL, PT, UK) and 3) those which have no CE with this denomination, although they have centres with all the characteristics of a CE. Genetic tests are offered internationally, through both public and private sector genetic testing services. Currently, 956 laboratories offering tests for 1,559 genes are registered with Orpha.net in Europe at large. The test offer differs greatly from one large country to another: Germany (1,141 genes), France (874 genes), Italy (625 genes), Spain (582 genes), the UK (414 genes). However, with the introduction of next generation sequencing the disease-centered offers will gradually transform into targeted panel-based and/or exome-based diagnostics offers. According to available data, only testing for cystic fibrosis is provided by every European country. This situation explains the large cross-border flow of specimens, highlighting the need to provide access to services in other countries when necessary, especially for very rare diseases. Legal and financial issues concerning cross-border testing are not yet fully addressed. ESHG is a non-profit international body which aims to promote research in basic and translational aspects of medical genetics. It also facilitates contacts between all professionals, organizations and private entities which have similar goals. An overview of ESHG activities will be presented, together with examples from the genomics policy domain.

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WS-02. RD-Connect: A database for rare disorders research

Ivo Gut

Centro Nacional de Análisis Genómico (CNAG), Barcelona, Spain

Around 300 million people worldwide are estimated to suffer from one of the 6000+ known rare diseases. However, each of these rare diseases only affects a few individuals in each region and research initiatives, registries, biobanks and data repositories are usually highly fragmented and uncoordinated. Therefore, discovery is slowed down due to limited access to sufficient patients, high quality information and results.

For rare diseases research to advance requires a number changes in how things are done. Many issues need to be resolved, 1) the phenotypic description of patients is often vague, incomplete or focuses only on the phenotypic description of the disease related elements of the patient, 2) often patients are misdiagnosed as the treating physician has no prior reference due to the rarity of the disease, 3) patients are not

captured systematically, 4) in contrast to the cancer field the willingness of clinicians/researchers to share information or patient materials is limited, 5) genomic technologies nowadays provide exquisite resolution of genomes and, if used correctly help resolving many of the genetic causes underlying rare diseases. However, in many instances the way genomic technologies are applied is suboptimal, 6) Optimal study design and statistical rigor is not always taken care of.

The EU FP7-funded RD-Connect project is building a platform to harmonize and securely integrate databases, registries, biobanks, clinical bioinformatics and -omics data generated with standardized pipelines. Platform design has consisted of a formal use-case evaluation process performed in collaboration with potential clinical research users and the two main associated EU FP7-funded projects Neuromics and EURenOmics. This platform will collect rare disorders content systematically and provide a toolbox to analyze data in relation to the data held in the database. This will be described in this presentation.

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WS-03. RD-Neuromics: -omics research for diagnosis and therapy in rare neuromuscular and neurodegenerative diseases – an EU funded FP7 project

V Straub [1], A Aartsma-Rus [2], A Brice [4], K Bushby [1], E Cattaneo[5], B Corman [6], A Durr [4], A Ferlini [7], H Graessner [3], M Hanna [8], H-J Joosten [9], J Kirschner [10], T Klockgether [11], N Laing [12], N Levy [13], H Lochmüller [1], O Magnusson [14], F Muntoni [15], F Roos [16], D Rubinsztein [17], L Schöls [3], E Schwartz [18], H Stefansson [14], S Tabrizi [19], V Timmerman [20], C Turner [1], B Zurek [3], H Graessner [3], B Wirth [21], G-J van Ommen [2], **O Riess** [3] (on behalf of the Neuromics consortium: www.rd-neuromics.eu)

[1] *Newcastle University, UK;* [2] *Leiden University Medical Center, Netherlands;* [3] *Tübingen University, Germany;* [4] *Groupe Hospitalier Pitié Salpêtrière, Paris, France;* [5] *University of Milan, Italy;* [6] *Profilomic, Boulogne-Billancourt, France;* [7] *University of Ferrara, Italy;* [8] *MRC Centre for neuromuscular diseases, University College London, UK;* [9] *Bio-Prodict, Nijmegen, Netherlands;* [10] *University of Freiburg Medical Center, Germany;* [11] *University of Bonn, Germany,* [12] *University of Western Australia, Australia;* [13] *University of Aix-Marseille, France;* [14] *deCODE, Reykjavik, Iceland;* [15] *Institute for Child Health, University College London, UK;* [16] *Agilent Technologies, Uppsala, Sweden;* [17] *Cambridge University, UK;* [18] *Ariadne, Rockville, USA;* [19] *Institute of Neurology, University College London, UK;* [20] *University of Antwerp, Belgium;* [21] *University Hospital Cologne, Germany*

Neuromics is an EU-funded translational research project which has the primary aim of greatly improving understanding of neuromuscular and neurodegenerative diseases. The research will study around 1100 exomes from undiagnosed patients in its aim to discover novel disease-causing and disease-modifying genes and to identify potential new therapeutic targets. Partners have also undertaken deep-phenotyping of patients using human phenotype ontology (HPO) terms. Agreements are in place to allow the secure sharing of this standardised clinical information along with WES and other –omics data both within Neuromics and with the wider rare-disease field. This will encourage collaborative partnerships and speed progress towards therapeutic and diagnostic breakthrough and improvements in care for patients. The

project focusses on 10 rare, genetic neuromuscular and neurodegenerative disease groups: frontotemporal lobe degeneration; Huntington's disease; ataxia; hereditary spastic paraplegia; spinal muscular atrophy and lower motor neuron disease; hereditary motor neuropathy; congenital myasthenic syndrome; muscular dystrophy and muscular channelopathy. The project brings together the leading research groups in Europe, five highly innovative SMEs and overseas experts to work together using the most sophisticated -omics technologies employing genomics, transcriptomics, proteomics and metabolomics.

The consortium is coordinated by Olaf Riess at Tübingen University, Brunhilde Wirth at Cologne University and Gert-Jan van Ommen at Leiden University. Neuromics is working closely with RD-Connect, the rare-disease platform, in order to develop a global infrastructure for the wide sharing of research outputs of Neuromics, and other rare disease projects. At the end of its first year of activity, this poster describes the aims and methods used in the Neuromics project and reports on progress made so far. It highlights how Neuromics will contribute significantly to the ambitious goals of the International Rare Diseases Research Consortium (IRDiRC): deciphering the genetic causes of all rare diseases and the development of 200 new therapies by 2020.

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WS-04. Pharmacogenomics Initiatives : eMoDiA

T Katsila, G P Patrinos

University of Patras School of Health Sciences, Department of Pharmacy, Patras, Greece

electronic **Mo**lecular **Di**agnostics **A**ssistant (eMoDiA) points out that the refined diagnosis and hence, the choice of personalized therapy are the key initiatives of this effort. Decoding the genome will aid the description of the connections between genetic profiles (both genetic variations and genes) and clinical phenotypes, aiming to model the complex biological information processes in disease. In turn, this will result in a quantitative and at the same time, predictive outcome of genotype to phenotype linkages. No doubt, this implies the production and analysis of huge heterogeneous clinical and molecular datasets and thus, the accommodation and deployment of advanced information technologies. eMoDiA, in this way, offers the grounds for pharmacogenomics to meet the current challenges of personalized medicine. Upon successful completion, a personal genetic smart-card will be designed and developed to serve the secured access to sensitive clinico-genomic/-genetic data. The benchmark clinical domains of eMoDiA are bipolar disorder and amyotrophic lateral sclerosis.

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WS-05. Towards an electronic PharmacoGenomics Assistant (ePGA)

G Potamias

Foundation of Research and Technology Hellas, Institute of Computer Science, Biomedical Informatics laboratory, Heraklion, Crete, Greece

We present the design and development of an integrated electronic PGx Assistant (ePGA) that provides personalized genotype-to-phenotype PGx translation

[67]

services. Translation is based on the 'matching' of individual genotype (SNP) profiles against PGx gene haplotypes, and the subsequent inference of the corresponding metabolic phenotypes. Currently ePGA employs harmonized haplotypes-tables from PharmGKB (www.pharmgkb.org) and DMET™ Plus. Besides personalized translation, ePGA provides services for: (i) the delivery of respective personalized drug recommendation, (ii) the retrieval of PGx information regarding (pharmaco)gene-variants and drugs, and (iii) update of PGx-related information on newly discovered gene-variants. The initial web-based implementation of the system is shown.

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WS-06. Pharmacogenomic Translation Service

E Kartsaki

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We present the personalized genotype-to-phenotype PGx translation service of the eMoDiA's ePGA system. The inclusion of a personalized PGx translation component is founded on the assumption that "*clinical high-throughput and pre-emptive genotyping will eventually become common practice and clinicians will increasingly have patients' genotypes available before a prescription is written*". The PGx translation service infers metabolic phenotypes (extensive, intermediate, poor/ultra) from individual genotype (SNP) profiles. A special allele-matching algorithmic process is utilized and appropriately customized. For each pharmacogene, and based on available haplotype/allele tables, an individual's genotype-profile is matched against the available gene-alleles. Each inferred diplotype is assigned to a metabolic phenotype, according to available "look up" tables. The initial web-based implementation of the service is shown.

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Ws-07. A Pharmacogenomics Dashboard of 1000 Genomes Project

K Lakiotaki

Foundation of Research and Technology Hellas, Institute of Computer Science, Biomedical Informatics laboratory, Heraklion, Crete, Greece

The availability of extensive genotype data from the 1000 Genomes Project (1kG) has opened the floodgates to researchers to study human genetic variation in several research areas, including pharmacogenomics (PGx). Here we utilize PGx translation methods and tools developed during the design and implementation of eMoDiA's electronic PGx Assistant (ePGA). We applied the translation methodology on the 1kG 1,092 samples, which are distributed among fourteen different populations. We focus on 69 pharmacogenes (related to about 200 drugs), and target 500 respective SNP biomarkers. By analyzing these 500 SNP biomarkers we assigned a PGx gene-specific PGx metabolic profile (phenotype) to every individual sample. Among other findings, the analysis shows that metabolic profiles differ significantly among 1kG populations in most (~75%) of the studied pharmacogenes.

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CORPORATE LECTURE

PL-15. Targeted locus Amplification

Max van Min

Cergentis, Utrecht, the Netherlands

Current methodologies in genetic diagnostics and genetic research are limited in their ability to uncover all possible genetic variation in genes of interest. Clinical genetic tests, for example, often only focus on exons, the coding parts of the gene, and therefore miss variants in the non-coding regulatory sequences of genes (promoters and enhancers) that can also disrupt gene function. In addition, structural variants, i.e. deletions/ duplications (CNVs), translocations, insertions and inversions, are difficult to uncover. Their robust detection is hampered by the hypothesis-driven nature of current targeted re-sequencing methodologies: the collection of probes (in hybridization-based capture methods) or primers (in polymerase or ligase-based re-sequencing approaches) determines the sequences that will be analyzed. Unknown sequences, per definition introduced by chromosomal rearrangements, are therefore difficult to capture and re-sequence with these methods. None of the existing methods allows for haplotyping, ultimately needed to get complete sequence information. Here we present targeted locus amplification (TLA), a strategy to selectively amplify and sequence entire genes based on the cross-linking of physically proximal sequences and is based on crosslinking, fragmenting and religation steps such as performed in chromatin capture technologies. We show that, unlike other targeted re-sequencing methods, TLA works without detailed prior locus information as one or a few TLA primer pairs are sufficient for sequencing tens to hundreds of kilobases of DNA. This, we demonstrate, enables robust detection of single nucleotide variants, structural variants and gene fusions in clinically relevant genes. TLA can also be used for haplotyping large chromosomal intervals and for characterizing the insertion sites and sequences of integrated transgene and viruses. The TLA Technology was developed by Cergentis, a spin-off from the Royal Academy of Sciences in the Netherlands. In the presentation Max van Min will also briefly describe the process of setting up a company and provide some insights in the differences between working in an academic position and a company.

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BEST ABSTRACTS

BA-01. Studying the effect of L-cysteine in MELAS and MERRF

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Mitochondrial disorders comprise a large group of heterogeneous disorders characterized by impaired cellular energy production. Mutations located within the mt-tRNA genes are a common cause of mitochondrial disorders. We have previously reported that the symptoms in reversible infantile respiratory chain deficiency (RIRCD), and reversible infantile hepatopathy, could be explained by low thio-modification of the mt-tRNA[Glu] by TRMU. Since the availability of cysteine (which is crucial for normal TRMU activity) in the neonatal period is limited by the low activity of the cystathionase enzyme, dietary cysteine intake may be very important at this age. RIRCD myoblasts showed low activities, however adding L-cysteine to the culture medium fully reversed this defect. Furthermore, L-cysteine prevented the decrease of mitochondrial translation in TRMU deficient cells, TRMU down-regulated RIRCD cells and controls, further supporting the hypothesis that low cysteine concentrations may play a role in triggering a reversible in vitro mitochondrial translation defect. Two other mutations m.3243A>G and m.8344A>G also lead to impaired post-transcriptional modifications, such as thiolation and taurino-methylation, of mitochondrial tRNAs for Leu and Lys and lead to MELAS and MERRF respectively. The pathogenic mutation m.3243A>G in tRNA[Leu], results in lack of taurine modification at the wobble position of the tRNA, leading to reduced UUG (Leu) translation and complex I deficiency. The pathogenic mutation of m.8344A>G, results in reduced thiolation and taurine wobble modification- of tRNA[Lys] which leads to mitochondrial dysfunction. We hypothesized that L-cysteine might have beneficial effect in these patient cells carrying the mutations. In this study, we supplemented MERRF and MELAS cells from patients with L-cysteine and consequently we investigated mitochondrial complex assembly by BN-PAGE, oxygen consuption and "in gel" activities. Our data indicated increased levels of mitochondrial complexes after L-cysteine supplementation both in the control and in the patients' cells.

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BA-02. Next-generation sequencing analysis of hematological malignancies: Serbian experience

<u>S Pavlovic</u> [1], B Stanic [1], J Kostic [1], N Pejanovic [1], B Lucic [1], N Tosic [1], I Glumac [1], D Janic [2,3], L Dokmanovic [2,3], S Jankovic [2,3], N Suvajdzic Vukovic [3,4], D Tomin [3,4], B Mihaljevic [3,4], M Todorovic [3,4], J Jelicic [3,4], D Krstajic [1], M Popovic [5], I Bogicevic [5], M Stojiljkovic [1]

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Rare diseases (RD) are life-threatening, chronically debilitating conditions, affecting less than 1 in 2000 people. 7-10 % of people have one of the 6000–8000 estimated RD, accounting for approximately 500000 individuals in Serbia. Most of RD are genetic in origin, including hematological malignancies. Next-generation sequencing (NGS) platforms have completely revolutionized the way of studying diseases at the genome, transcriptome and epigenome level. Here we describe the use of NGS TruSeq Amplicon Cancer Panel to screen mutational hotspots in 48 cancer-related genes. We sequenced 95 samples from patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia and CNS lymphomas using MiSeq. We found polymorphic variants in TP53, RET, EGFR and GNA11 genes present in the majority of samples; SMO, NOTCH1, RB1 and HRAS genes in leukemias; FGFR3, CSFR1, GNA11, JAK3 and SMARCB1 genes in lymphomas. We detected an insertion in the NPM1 gene (chr 5: 170837543) only in adult AML and a deletion in the HRAS gene (chr 11: 534398) in AML. This study was the first to apply NGS of cancer genes in Serbian population, prompting further investigation for local founder mutations and variants.

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FLASH TALKS

FT-01. The first extracellular loop of the PTCH1 protein: a true "hot spot" for PTCH1 gene?

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Background: Nevoid basal cell carcinoma syndrome (Gorlin syndrome) is a rare autosomal dominant disorder characterized by numerous basal cell carcinomas, odontogenic keratocysts of the jaws and diverse developmental defects. This disorder results from mutations in Patched 1 (PTCH1) gene, a human homologue of Drosophila segment polarity gene Patched. More than 230 mutations were described, showing slight clustering within the first and second extracellular loop of the PTCH protein. In this study we analyzed two Serbian patients with Gorlin syndrome.

Methods: Peripheral blood or buccal swab were used for DNA extraction, as well as tumor tissue from the patient I. Direct sequencing of 23 coding exons of PTCH1 gene was performed. Family members, as well as five healthy controls were also included in this study.

Results: A novel frameshift mutation in exon 6 of PTCH1gene (c.903delT) has been detected in the first patient. This loss-of-function mutation is leading to synthesis of truncated, probably nonfunctional protein. The mutation was not transmitted to progeny and was not detected in healthy subjects. In addition, a frameshift mutation in exon 21 (c.3524delT) was detected in tumor-derived tissue sample of the patient. The analysis of the second patient showed the presence of point mutation in exon 8 (c. 1148 C>A). The same nonsense mutation was also present in two affected family members, but was not detected in healthy individuals.

Conclusion: Screening of all coding exons of PTCH1 gene in our patients with Gorlin syndrome revealed two novel germline mutations, and one novel somatic mutation present in tumor tissue of the patient I. The germline mutations were in heterozygous state and were not detected in healthy subjects, suggesting that they are de novo disease-causing mutations. Both somatic mutations affect the first extracellular loop of PTCH protein, thus supporting previous evidence that it is a "hot spot" for this gene.

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FT-02. High WT1 expression as a new molecular marker of poor prognosis in Serbian Acute Myeloid Leukemia patients with normal karyotype (AML-NK)

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AML-NK represents the biggest group of ALM patients (pts) classified with intermediate prognosis. Constant effort has been made in the direction of introducing new molecular markers with prognostic significance for further, more precise, risk stratification. The Wilm's tumor gene (WT1) expression level has been suggested as a new possible prognostic marker. The aim of our study is to evaluate the WT1 expression levels at diagnosis and during follow-up of the disease in AML-NK pts, and to investigate its association with other molecular and clinical data. Fresh bone marrow (BM) samples were collected from 53 AML-NK pts at diagnosis, and 45 samples were collected during follow-up of the disease from 28 pts. WT1 expression level was quantified by RQ-PCR method. WT1 expression was significantly higher (mean 3698.25±1278.14, range 0.23-64142.81) in AML-NK pts compared to healthy controls (mean 3.00±1.13, range 0.06-11.53)(p<0.001). Using mean WT1 expression level at diagnosis as a cut-off-value, pts were divided into two groups with high or low expression. High WT1 expression was significantly associated with high WBC counts (p=0.04), high peripheral blood and BM blast percentage (p=0.001 and p=0.04, respectively). In addition, high WT1 expression was associated with the presence of FLT3 mutations (p<0.001) and NPM1 mutations (p=0.002), but not with IDH1 or IDH2 mutations. High WT1 expression had significant impact on prognosis i.e. lower complete remission rate (CR)(p=0.002), higher early death (ED) rate (p=0.03) and shorter overall survival (OS)(p=0.014). However, high WT1 expression didn't retain its prognostic significance in multivariate analyses. Among pts in CR, median WT1 expression was 14.99, range

2-81.46. Comparing this WT1 expression value with one detected at the beginning of the disease, we found that 11 pts had ≤2 log reduction, and 9 pts had >2 log reduction. Pts with >2 log reduction had longer DFS (25 vs. 8 months) and OS (27 vs. 10 months) but without statistical significance. In relapse samples (10 pts available) WT1 expression increased significantly (median 1525.04, range 60.13-4305.47). Median log increase in relapsed samples was 1.9, range 0.7-2.9. This study shows that high WT1 expression predicts low CR rate, tendency for ED and shorter OS in our cohort of pts. Likewise, determining the level of log reduction of WT1 expression in CR samples, can be useful for DFS and OS duration prediction. For more precise prognostic stratification, we suggest that WT1 expression should be included in the series of molecular analyses in AML-NK pts.

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FT-03. Characterization of the 22q11.2 region in patients with clinical features of 22q11.2 deletion syndrome

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22q11.2 deletion syndrome (22q11.2DS) is a shared name for several entities (DiGeorge syndrome, conotruncal anomaly face syndrome and velocardiofacial syndrome). This is the most common deletion disorder in humans with an estimated incidence of approximately 1/4000 per live births. The clinical spectrum of the 22q11.2DS is wide and more than 180 malformations and various behavioral psychiatric disturbances have been described in patients with this syndrome. Patients with 22q11.2 microdeletion syndrome may have any combination of the following features: cardiac defect, characteristic facial appearance, thymic hypoplasia, cleft palate/velopharyngeal insufficiency and hypoparathyroidism with hypocalcaemia. The purpose of this study was to characterize the 22q11.2 region in patients with phenotype resembling 22q11.2DS using fluorescence in situ hybridization (FISH) and high density multiplex ligation-dependent probe amplification (MLPA) kit. FISH analysis revealed 22q11.2 microdeletion in 24/57 (42.1%) patients. In 27 patients having no deletion detected by FISH, MLPA analysis was performed. MLPA enables better characterization of size and position of typical 22q11.2 deletions, detection of cryptic deletions of 22q11.2 region and analysis of another five genomic loci associated with phenotypes resembling 22q11.2DS. This analysis did not reveal 22q11.2 microdeletion in any of 27 patients. Furthermore, no atypical or cryptic deletions of 22q11.2 region were detected by MLPA in these patients. Additionally, in 13 out of 14 analyzed patients with 22q11.2 microdeletion previously confirmed by FISH, a deletion 3 Mb in size of typical deletion region was disclosed. In 1 out of 14 patients a small 1.5 Mb deletion of typical deletion region was found. Also, by MLPA we detected distal 4q deletion in a patient with clinical features resembling 22q11.2DS. In conclusion, taking into account wide variety of clinical phenotypes in our patient cohort, we stress the need for multidisciplinary assessment, including comprehensive clinical evaluation and genetic testing of all patients with suspected 22q11.2DS.

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FT-04. Antitumor effect of Meripilus giganteus Karst. methanolic extract via upregulation of p53, BAX and SOX1 expression in HeLa cells

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Cancer, the second leading cause of death worldwide, is characterized by uncontrolled cellular growth, local tissue invasion and distant metastases. Besides their high nutritional value, mushrooms possess a wide variety of beneficial effects on human health, with special emphasis on pharmacological properties such as antioxidant, antimicrobial and antitumor activities. The aim of this study was to investigate phenolic profile and antimicrobial activity of Meripilus giganteus Karst. methanolic extract, as well as to test its cytotoxic effect on HeLa cancer cell line and to determine cellular targets involved in cytotoxic action of the extract. M. giganteus was subjected to extraction with methanol in order to obtain

methanolic extract for further analysis. Phenolic acids were determined by ultra fast liquid chromatography. Antimicrobial activity was tested by modified microdilution method. Cytotoxic activity on HeLa cells was assessed by MTT assay. Morphological changes of control and treated HeLa cells were analyzed by DAPI/PI staining. Expression of apoptosis-related proteins was analysed by Western blot.

Three phenolic compounds were identified in the M. giganteus methanolic extract: p-coumaric (24.19 μg/g), p-hydroxybenzoic (10.06 μg/g) and cinnamic (3.39 μg/g) acids. Regarding antibacterial and antifungal activity, Staphyloccocus aureus and Aspergillus versicolor were the most sensitive species. Concentrations of extract required for 50% inhibition of growth of HeLa cells were 0.70 mg/mL and 0.41 mg/mL for 24 and 48 h of treatment, respectively. Cells treated with M. giganteus extract exhibited typical features of apoptosis such as nuclear condensation, fragmentation and formation of apoptotic bodies. Treatment of HeLa cells with the extract caused an increase in p53 and Bax protein levels and apoptosis-specific cleavage of PARP-1. Furthermore, an increase in SOX1 protein level was observed upon treatment with the extract.

M. giganteus is promising source for cancer chemoprevention, and might have application in the development of new drugs. We have shown for the first time that one of the mechanisms responsible for inhibition of cell growth of cervical cancer cells by M. giganteus extract relies on induction of apoptosis which is mediated through upregulation of p53. Additionally, antitumor effect of M. giganteus extract might be mediated by upregulation of SOX1 tumor suppressor gene.

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FT-05. *SOX14* expression during retinoic acid induced neural differentiation of pluripotent embryonal carcinoma stem cells

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SOXB/SoxB group members of transpcription factors are of particular interest since they play a major role in neural development. Based on sequence analysis and functional studies in vertebrates SOXB/SoxB genes are further divided into subgroup B1, comprising activators (Sox1, Sox2 and Sox3) and subgroup B2, consisting of repressors (Sox14 and Sox21). SOX14/Sox14 gene is one of the evolutionary most conserved SOX genes, and lack of any known mutated phenotype suggests that it might have an essential role during development. Sox14 gene expression analysis during development of mouse and chick suggest that its expression pattern is restricted to a limited population of interneurons in the developing brain and spinal cord.

In our present study we have analyzed expression of the SOX14 gene during retinoic acid induced neural differentiation of human (NT2/D1) and mouse (P19) pluripotent embryonal carcinoma stem cells. We have demonstrated that SOX14 was expressed at low level in both NT2/D1 and P19 cells and its expression was increased during retinoic acid induced neural differentiation. The level of SOX14 expression was downregulated in NT2-N compared to NT2 4W, both on protein and mRNA levels, while its expression was

upregulated in the P19-N population compared to P19 EB. While all MAP2+ neurons in NT2-N were SOX14 positive, 5% of MAP2+ neurons were SOX14 negative in P19-N. Interestingly, we also observed that the level of SOX14 expression was lower in terminally differentiated MAP2+ neurons comparing to large flat non-neuronal cells. For the first time our analysis of SOX14 expression on single cell level revealed that it is expressed in neuronal as well as in non-neuronal differentiated derivatives. Obtained results contribute to better understanding expression of SOX14/Sox14 during in vitro neural differentiation and further analysis is needed to reveal its precise role during this process.

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FT-06. SOX2 overexpression affects neural differentiation of human pluripotent NT2/D1 cells

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SOX2 is one of the key transcription factors involved in maintenance of neural progenitor identity. However, its function during the process of neural differentiation, including phases of lineage-specification and terminal differentiation is still poorly understood. Considering growing evidence indicating that SOX2 expression level must be tightly controlled for proper neural development, the aim of this research was to analyze the effects of constitutive SOX2 overexpression on outcome of retinoic acid (RA) induced neural differentiation of pluripotent NT2/D1 cells. We demonstrated that in spite of constitutive SOX2 overexpression, NT2/D1 cells were able to reach final phases of neural differentiation yielding both neuronal and glial cells. However, SOX2 overexpression reduced the number of mature MAP2-positive-neurons while no difference in the number of GFAP-positive-astrocytes was detected. In-depth analyzes at single cell level showed that SOX2 downregulation was in correlation with both neuronal and glial phenotype acquisitions. Interestingly, while in mature neurons SOX2 was completely downregulated, astrocytes with low level of SOX2 expression were detected. Nevertheless, cells with high level of SOX2 expression were incapable to enter in neither of two differentiation pathways, neurogenesis nor gliogenesis. Accordingly, our results indicate that fine balance between undifferentiated state and neural differentiation depends on SOX2 expression level. Unlike neurons, astrocytes could maintain low level of SOX2 expression after they acquired glial fate. Further studies are needed to determine whether differences in the level of SOX2 expression in GFAP-positive-astrocytes are in correlation with their self-renewal capacity, differentiation status and/or their phenotypic characteristics.

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FT-07. Functional characterization of novel dominant-negative mutant of the human SOX18 protein

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Background: SOX18 protein is involved in a range of biological processes such as vasculogenesis, hair follicle development, lymphangiogenesis, atherosclerosis and angiogenesis.. Literature data show that interfering with SOX18 function inhibits blood vessel formation and subsequent tumor growth. Therefore, this gene is identified as a potential target for anti-angiogenic cancer therapy. Furthermore, it was suggested that dominant-negative SOX18 mutant could be considered as potential agent for antiangiogenic therapy. We generated and functionally characterized novel dominant-negative mutant of human SOX18 protein, together with wild-type counterpart.

Methods: Using the straightforward restriction enzyme digestion of SOX18 cDNA clone, we have generated construct expressing truncated SOX18 protein (pCISOX18DN). Ectopic expression of generated SOX18 constructs in HeLa cells was analyzed by Western blot analysis. Binding ability of proteins expressed from pCISOX18wt and pCISOX18DN were tested in electrophoretic mobility shift assays (EMSA) with oligonucleotide probe that contains three SOX consensus binding sites, designated as 3SX. Trans-activation properties of SOX18 protein expressed from genetared constructs were analyzed in luciferase assays.

Results: Wild-type and truncated form of SOX18 are efficiently expressed in HeLa cells and able to bind to their consensus sequence in vitro. Functional analysis confirmed that SOX18wt has potent trans-activation properties, while SOX18DN displayed dominant-negative effect.

Conclusion: Generated SOX18 expression constructs could be successfully used for further characterization of this protein function. This opens the possibility of pharmacological manipulation of this gene expression to stimulate or inhibit angiogenesis, in particular tumor angiogenesis.

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FT-08. Inflammatory bowel disease in Serbian population: association of proinflammatory gene variants with the disease and their combined contribution in the prediction of disease development

B Stankovic [1], S Dragasevic [2], N Kotur [1], G Nikcevic [1], D Popovic [2,3], A Sokic-Milutinovic [2,3], S Lukic [2,3], T Alempijevic [2,3], M Krstic [2,3], S Srzentic [1], K Klaassen [1], B Zukic [1], T Milosavljevic [2,3], S Pavlovic [1]

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Inflammatory bowel disease (IBD) is complex disorder that comprises Crohn's disease (CD) and ulcerative colitis (UC). Results of GWAS showed that genes involved in cytokine signaling were among 100 different loci associated with IBD. For the first time, our group has genotyped Serbian IBD patients for variants in TNFα, IL-6, IL-1β and IL-1ra genes in order to reveal their association with IBD occurrence. Furthermore, we aimed to design probabilistic model for prediction of IBD development.

We genotyped 166 IBD patients and 101 healthy controls for TNF-α (-308G/A, -238G/A), IL-6 (-174G/C), IL-1β (-511C/T) and IL-1ra (intron 2 VNTRs) variants by PCR-RFLP. IBD group was divided into CD and UC subgroups. CD group was additionally genotyped for three common CARD15 gene variants (R702W, G908R, Leu1007insC). Data were analyzed using the Pearson chi-squared test or Fisher's exact test, when appropriate. For prediction of disease development, a Bayesian network model was designed and applied. Statistically significant difference in frequency of TNF-α -308A variant carriers in CD vs control (p=0.035), UC vs control (p=0.049) and CD vs UC group (p= 0.0001) was found. In CD group frequency of IL-6 GG genotype was significantly lower in comparison with control group (p=0.036). In both CD and UC group IL-1ra allele 2 carriers were more frequent compared to controls (p=0.012 and p=0.013 respectively). Our results confirmed strong association of CARD15 variants with CD (p=0.002). Data for TNF-α, IL-6, IL-1β, IL-1ra and CARD15 gene variants were also used to compute the probability of disease occurrence. Results showed that the disease development could be predicted with 69% (CD) and 61% (UC) accuracy when these gene variants were taken into account. These results showed that in Serbian population TNF-α, IL-6, IL-1ra and CARD15 variants are genetic factors that are of importance in IBD susceptibility and can be used for prediction of disease occurrence.

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FT-09. Molecular genetic markers as a base for administration of targeted therapy in acute promyocytic leukemia

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The first molecular targeted therapy was introduced in rare hematological malignancies. The development of all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) for the treatment of acute promyelocytic leukemia (APL) has shifted the strategy of treatment from conventional chemotherapy to cell differentiation. ATRA and ATO are orphan drugs, both meeting the requirements for an ideal therapeutics which eliminate early molecular pathogenetic events responsible for the disease. ATRA annuls the existence of differentiation block caused by the presence of t(15;17) chromosomal translocation and fusion of the PML and RARalpha genes. ATO degrades the PML-RARalpha fusion protein, and it causes differentiation and apoptosis of the APL cells.

In this study, reverse transcription polymerase chain reaction (RT-PCR) was used for detection of PML-RARalpha fusion transcripts in order to follow-up the course of the disease and the effectiveness of the treatment in adult APL patients. The patients were followed for at least 3 years. They underwent standard treatment for APL patients, the combination of ATRA and chemotherapy, during both induction and consolidation phase of treatment. Among 22 APL patients (8M/14F, mean age 39.5 years), 18 were PML-RARalpha negative after conslidation therapy and 17 of them stayed in a longlasting remission,

while 1 patient developed molecular relapse within 3 years. 4 patients were PML-RARalpha positive after completion of the consolidation therapy. Two of them were treated by ATO. The first one is in a longlasting remission, while the other expressed persistent molecular positivity, underwent allogenic bone marrow transplantation and is in a remission for 4 years. The results of this study showed that the absence of the PML-RARalpha fusion transcripts after completion of consolidation therapy and beyond, predicts stable longlasting remission. Introduction of molecular diagnosis and follow-up enabled the application of different orphan drugs and personalized therapeutic approach for APL patients in Serbia.

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FT-10. Application of mass spectrometry in forensic serology

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While forensic DNA profiling makes it possible to individualize biological evidence, the unambiguous identification of the body fluid from which the DNA was recovered itself can present forensic serologists with a significant challenge. For example, if a genetic profile generated from a swab of a male suspect's finger is consistent with that of an alleged female victim of sexual assault, more than one interpretation is possible. Current antibody- and enzyme activity-based assays used by forensic practitioners for biological fluid identification yield only presumptive results. Positive results with non-target body fluids or cross-reactivity with non-human sources has also been well documented. Some serological tests can consume unacceptable quantities of precious evidence while for other body fluids there are simply no available tests at all. For example, there is no reliable test for the presence of vaginal secretions and tests for blood do not allow the practitioners to distinguish between peripheral and menstrual blood.

This information, however, can often provide criminal investigators with critical context in regard to evidentiary material, Thus, there is clear value in developing more accurate and sensitive approaches for identifying biological stains. Using state-of-the-art protein characterization technologies, the proteomes for six body fluids (peripheral and menstrual blood, vaginal fluid, semen, urine and saliva) have been characterized and mapped. Through a comparative analysis of these proteomes, panels of high-specificity protein biomarkers have been compiled and tested for the accurate, reliable and confirmatory identification of bodily fluids commonly encountered in a forensic context. Current research has expanded this work by developing and validating a multiplex assay for the simultaneous identification of the six aforementioned biological fluids. The assay employs targeted ion multiple reaction monitoring (MRM) on a triple quadrupole mass spectrometer (QQQ). This facilitates highly selective and specific fluid identification from single as well as mixed source casework-type samples.

Validation of this multiplex assay has included sensitivity studies, reproducibility studies, repeatability studies and species specificity studies. Not only will this provide practitioners with greatly

improved tests for human body fluids but the multiplex design eliminates the need to perform separate assays on a single item of evidence.

In short, this research will provide the forensic community with a robust assay for the confirmatory identification of human biological stains – especially those typically encountered in connection with sexual assault and homicide evidence.

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FT-11. A physician's perspective on direct-to-consumer genetic testing

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Since several years the direct-to-consumer genetic testing (DTC) became available for patients due to the decreasing cost of genome sequencing. Therefore, it is highly probable that physicians in the near future will encounter patients, who wish to discuss the DTC test results and ask for a medical advice concerning their disease risk profile. To meet the need of the patients, understanding of DTC will be required among physicians. The aim of this study is to evaluate the general knowledge, awareness and experience of physicians concerning the DTC. Furthermore, we assess the willingness in further education and the barriers in improving their expertise and skills regarding this issue. For this purpose we designed and conveyed a survey among the residents and attending physicians in the department of internal medicine of two large hospitals in Switzerland.

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FT-12. Genetic variation as a predictor of smoking behavior

N Flora [1], S Tsikrika [2], C Chalikiopoulou [1], A Tavianatou [1], S Vakali [2], Z Lanara [1], O Giannakopoulou [1], E Dalabira [1], O Leukaditi [1], M Koromina [1], A Vozikis [3], T Giannakopoulos [2], T Katsila [1], C Gratziou [2], G P Patrinos [1]

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Smoking is a major public health problem and is the single largest cause of preventable death in the world, contributing to >5 million deaths a year. The persistence of smoking can be attributed to multiple diverse causes, yet genetic risk factors contribute to smoking behavior, accounting for approximately (i) 40–75% of the variation in smoking initiation, (ii) 70-80% of the variation in smoking maintenance and (iii) about 50% of the variance in cessation success. Herein, we investigated the correlation of genomic variants with smoking addiction, smoking initiation or smoking cessation. Genomic DNA was isolated from saliva, following the informed consent of 90 smokers and 75 non-smokers of Hellenic origin. We have subsequently genotyped these individuals focusing on the rs1329650 in the *CHRNA3* gene, as it has been previously correlated with nicotine

dependence and notably, each additional copy of a risk allele corresponded to an increase in smoking quantity. Furthermore, rs6265 in the *BDNF* gene (where each additional copy conferred an increase in the relative risk of regular smoking) and rs3025343 in *the DBH* gene (where each additional copy conferred a decrease in the relative risk of regular smoking) were investigated, as they have been previously correlated to smoking initiation and cessation, respectively. Our findings show that there is statistically significant difference for the rs1329650 and rs6265, between smokers and non-smokers. These variants may constitute genomics biomarkers for smoking behavior.

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FT-13. Heterogeneous genetic alterations in sporadic nephrotic syndrome associate with resistance to immunosuppression

A Provenzano [1], B Mazzinghi [2], F Becherucci [3], L Giunti [2], G Sansavini [3], F Ravaglia [3], R M Roperto [3], S Farsetti [3], E Benetti [4], M Rotondi [5], L Murer [4], L Lasagni [6], M Materassi [3], P Romagnani [1,3,6], S Giglio [1,2]

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In children, sporadic nephrotic syndrome can be related to a genetic cause, but to what extent genetic alterations associate with resistance to immunosuppression is unknown. In this study, we designed a custom array for next-generation sequencing analysis of 19 target genes, reported as possible causes of nephrotic syndrome, in a cohort of 31 children affected by sporadic steroid-resistant nephrotic syndrome and 38 patients who exhibited a similar but steroid-sensitive clinical phenotype. Patients who exhibited extrarenal symptoms, had a familial history of the disease or consanguinity, or had a congenital onset were excluded. We identified a genetic cause in 32.3% of the children with steroid-resistant disease but zero of 38 children with steroid-sensitive disease. Genetic alterations also associated with lack of response to immunosuppressive agents in children with steroid-resistant disease (0% of patients with alterations versus 57.9% of patients without alterations responded to immunosuppressive agents), whereas clinical features, age at onset, and pathologic findings were similar in patients with and without alterations. These results suggest that heterogeneous genetic alterations in children with sporadic forms of nephrotic syndrome associate with resistance to steroids as well as immunosuppressive treatments. In these patients, a comprehensive screening using such an array may, thus, be useful for genetic counseling and may help clinical decision making in a fast an d cost-efficient manner.

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FT-14. Therapeutic implications of novel mutations of *RFX6* gene associated with early-onset diabetes

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Identification of the genetic defect underlying early-onset diabetes is important for determining the specific diabetes subtype, which would then permit appropriate treatment and accurate assessment of recurrence risk in offspring. Given the extensive genetic and clinical heterogeneity of the disease, high throughput sequencing might provide additional diagnostic potential when Sanger sequencing is ineffective. Our aim was to develop a targeted next generation assay able to detect mutations in several genes involved in glucose metabolism. All 13 known MODY genes, genes identified from a genome-wide linkage study or genome-wide association studies (GWAS) as increasing the risk of type 2 diabetes and genes causing diabetes in animal models, were included in the custom panel. We selected a total of 102 genes by performing a targeting resequencing in 30 patients negative for mutations in the GCK, HNF1α, HNF4α, HNF1β and IPF1 genes at the Sanger sequencing analysis. Previously unidentified variants in the RFX6 gene were found in three patients and in two of them we also detected rare variants in WFS1 and ABCC8 genes. All patients showed a good therapeutic response to dipeptidyl peptidase-4 (DPP4) inhibitors. Our study reveals that next generation sequencing provides a highly sensitive method for identification of variants in new causative genes of diabetes. This approach may help in understanding the molecular etiology of diabetes and in providing more personalized treatment for each genetic subtype.

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FT-15. Screening of *CYP1B1* gene in Tunisian patients with primary congenital glaucoma

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Primary congenital glaucoma (PCG) is a childhood autosomal recessive disorder caused by developmental defects in the trabecular meshwork and anterior chamber angle. It caused predominantly by mutations in the CYP1B1 gene. In this study we plan to sequence the CYP1B1 gene to identify its mutation profile in the Tunisian primary congenital glaucoma patients. Forty unrelated PCG patients and 100 randomly selected Tunisian individuals, with senile cataract, served as controls were enrolled in the study. DNA sequencing was done by an autosomal DNA

sequencer (ABI model 377; PE-Applied Biosystems). Six different mutations were detected: G61E, g.4339delG, P52L, G90R, F440C and G329D (G90R and F440C were novel mutations). They affected conserved regions of the CYP1B1 gene. G61E and g.4339delG were associated with the severe disease phenotype especially at homozygous state. Ten different SNPs were also detected in the promoter, non-coding (exon1) and coding (exon 2 and 3) regions. Our results confirm that: 1) Mutations in CYP1B1 are a major cause for PCG in our patients. 2) Identifying of G61E and g.4339delG particularly among severe disease is of clinical significance. 3) G90R and F440C were identified as novel mutations in our study. 4) There is a very strong association of the promoter SNP rs2567206 with PCG. The other promoter SNPs also exhibit significant association but are not strong enough as evident from the odds ratios and the 95% confidence intervals. 5) The haplotype analysis with the promoter variant rs2567206 and the coding region indicates a risk haplotype as was seen in other populations. The other haplotypes are protective in the Tunisian cohort.

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FT-16. Pharmacoepigenomic analysis of *MAP3K5* gene promoter in β-type hemoglobinopathies patients under hydroxyurea treatment

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MAP3K5 (ASK1), a member of the MAPK family, is located on chromosome 6q23 and involved in the MAPK pathway. Our previously published observations (1) have revealed that a short tandem repeat (STR) in the promoter and two intronic Single Nucleotide Polymorphisms (SNPs) of the gene are associated with low HbF levels and β-thalassemia disease severity. As far as it is known, epigenetic modifications (activation or suppression of DNA methylation, miRNA-mediated post-transcriptional processes and histone acetylation) regulate gene expression.

Our study aims to investigate whether the DNA methylation levels of the *MAP3K5* promoter (CpG islands) correlates to the *MAP3K5* gene expression levels. For this, we employed a pyrosequencing-based methylation assay. Particularly, the CpG assay was performed following the manufacturer's instructions (Qiagen). The study region corresponded to 20 bases upstream of the *MAP3K5* promoter STR ($\dot{}$5-GCGCG-$\dot{}$3) up to $\dot{}$5-UTR of the gene. Our analysis included the following groups: healthy controls, Non Transfusion Dependent Thalassemia (NTDT) patients and β-thalassemia major patients.

No DNA methylation was observed in the *MAP3K5* promoter CpG islands, when NTDT and β-thalassemia major patients were compared to healthy individuals (on the basis of pyrograms).

Our findings indicate that the DNA methylation of the *MAP3K5* promoter is most likely not correlated with the *MAP3K5* gene expression.

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FT-17. Differential molecular profiling of human hematopoietic tissues during human ontogenesis - A β-type hemoglobinopathies therapeutics approach

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Hemoglobinopathies result from genetic abnormalities (both quantitative and qualitative) in the hemoglobin molecule production. They are the commonest single gene disorders worldwide. Different types of hemoglobin molecules are known to be produced during the embryonic, fetal and adult erythropoiesis. During the fetal stage, fetal hemoglobin (HbF) production is expressed at high levels, whereas it gradually declines afterwards reaching less than 2% of total hemoglobin shortly after birth. In the clinic, HbF high levels improve the clinical symptoms of β-thalassemia or sickle cell disease (SCD) patients. In humans, the increased HbF production and the switch from fetal to adult hemoglobin are controlled by various regulatory factors, by a mechanism that still remains elusive.

A whole transcriptome analysis was employed aiming to identify the transcription profile of human hematopoietic tissues in different stages of ontogenesis. For this, ex vivo human erythroid progenitors from adult peripheral blood have been isolated and cultured in comparison to umbilical cord blood and human fetal liver. Total RNA was isolated from erythroid progenitor cells and then, labeled and hybridized to the Affymetrix Human Genome U133 array. The differential expression of probe sets among the hematopoietic tissues considered was discriminated by AltAnalyze software.

Our comparative analysis included three different groups; umbilical cord blood versus adult peripheral blood, fetal liver versus adult peripheral blood and umbilical cord blood versus fetal liver versus adult peripheral blood. Ours results indicate that 165 genes were differentially expressed between the first group, 1239 genes were differentially expressed in the second group and finally, 348 genes were differentially expressed between high (umbilical cord blood and fetal liver) and low HbF expressing tissues (adult peripheral blood), indicating that these genes may be implicated in potentiating HbF levels.

Our findings, being further supported by our previously published observations (1,2), hold promise towards the identification of unique molecular pathways involved in HbF production. These will subsequently be exploited in β-thalassemia patients' stratification and possibly in individualization of β-type-hemoglobinopathies therapeutics.

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FT-18. Pharmacogenomics in Europe: Applications in public health

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Pharmacogenomics in clinical practice is still challenging and hence, limited. Nevertheless, several countries are currently interested in studying and integrating pharmacogenomics into their public health systems. This study aims to examine and compare the genome structure of ten European populations in regards to pharmacogenomic biomarkers and their incidence. Our approach refers to data from several countries; Greece, Malta, Turkey, Croatia, Serbia, Slovenia, Czech Republic, Poland, Hungary and Germany. These populations were further divided into subgroups according to their history and geography standards; (i) Balkans (Greece, Croatia, Serbia, and Slovenia), (ii) Central (Hungary, Slovenia, Poland, Czech Republic and Germany) and (iii) Southern Europe (Greece, Malta, Turkey). A total of 1936 pharmacogenomic biomarkers in 235 genes with pharmacogenomic interest were investigated in 50 healthy individuals from every population in question by DMET+ microarray (Affymetrix, Santa Clara, CA, USA). We focused on the study of those pharmacogenomic biomarkers, sharing a frequency of 20% -50% (neither too rare, nor too frequent). After a thorough statistical analysis, we revealed that 123 pharmacogenomic candidate biomarkers correspond to the subgroup of South Europe, while 103 potential biomarkers were obtained when the subgroup of Balkans was examined. The subgroup of Central Europe resulted in 106 pharmacogenomic candidate biomarkers. A vast convergence was observed among countries. We feel that this study greatly contributes towards the integration of pharmacogenomics into the public health systems of Europe, with the aim of patient stratification and a favorable cost-benefit analysis.

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FT-19. Whole genome sequencing analysis of a Greek family affected by Adamantiades-Behcet disease

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Introduction: Adamantides-Behcet disease (or also called the 'silk road disease') was first described in 1930 by Benediktos Adamantiades. Usually, the Behcet's disease is presented in adulthood and it is rarely found in pediatric patients. It is more common in the Mediterranean and East populations, therefore is also called Silk Road Disease. The aim of this study was to search in depth the whole genome of a family that includes a child diagnosed with Behcet-Adamantiades disease and investigate further on the genes invloved in the disease and its complications.

Methods: The whole genome of all four members of a family [father, the mother, the child affected by Behcet-Adamantiades disease (male) and the other child (female) not affected by Behcet-Adamantiades disease] of Greek Origin (Northern Greece) was studied. Written consent was obtained from the parents in order to proceed with the analysis of the saliva samples of all four members of the family. A medical history, blood analysis and interview of the family was recorder. The first step in data analysing was to identify all the variants found in the Behcet Family and Control. Using the Master Variant file of each genome, a list of non -redundant variants

was generated using cgatools. The list of non-redundant variants was used to determine their presence in the selected genomes. The end result was a list of variants containing their position and how they are found in each genome.

Results: The results were divided in two parts: a) Genes found in the children and inherited by the parents. Description of the genes found in the whole genome of all four members of the family. b) Genes found in the son and not inherited by the parents. We have found 1745 variation type in the father, 1751 in the mother, 1781 in the child affected by the Behcet Disease and 1758 in the other child of the family. Our analysis was based on three models: the Xlinked model, the Recessive model and the De Novo model. Our results consisted of a variety of *de novo* mutations, of a list of X-linked mutations in the child affected by Behcet disease and also a number of genes and mutations inherited by both parents in both children. **Discussion:** this study is the first one to our knowledge to examine the whole genome of an entire family that includes a member diagnosed with Behcet-Adamantiades disease. Important results arose from the analysis of the whole genome and suggest that the use of the whole genome sequencing in clinical practice could help in the diagnosis and treatment of the disease.

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FT-20. Identification of genomic variants leading to Amyotrophic Lateral Sclerosis in the Hellenic population using a whole genome sequencing approach

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Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease, however it is estimated that 39,863 people in Europe, suffer from it, at the moment.

After testing a group of Greek ALS patients for the most commonly associated genes (SOD1, TARDBP and FUS/TLS) without coming across any mutations, we obtained the whole genome sequence of 10 of these patients, 5 diagnosed with definite ALS and 5 with probable familial ALS, using a fresh and accurate sequencing method based on DNA nanoball arrays and combinatorial probe-anchor ligation reads. To delineate the genetic causes underlying the Greek ALS phenotype, we further investigated the Whole Genome Sequencing findings, using three simple approaches; first, we run a comparison of the 10 patients' genomes against 5 Greek controls' genomes. This approach resulted in 174 common polymorphisms from which 6 were chosen for further investigation. Our second approach included the juxtaposition and subsequent comparison of our sequencing data with the Human Gene Mutation Database (HGMD). From this approach a 3'UTR FUS variation stood out. However, according to previous reports, it was not associated with the disease. Finally, the annotation of all the novel variants was performed and two of them, corresponding to the SLC36A1 and FGF13 genes were chosen for further investigation. The complexity of the ALS pathophysiology seems to demand a next generation method to reveal the genetic component of the disease as well as the genotype to phenotype associations.

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FT-21. Clinical-pharmacogenetic model for prediction of treatment outcome in malignant mesothelioma

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Background: Malignant mesothelioma (MM) is an aggressive cancer with poor prognosis. Most patients are treated with gemcitabine/cisplatin or pemetrexed/cisplatin chemotherapy, but both clinical characteristics and genetic variability may contribute to large interindividual differences in treatment outcome. Our aim was to construct and validate clinical-pharmacogenetic prediction models of outcome of gemcitabine/cisplatin or pemetrexed/cisplatin treatment and to develop an algorithm for genotype-based treatment recommendations.

Patients and methods: In total, 169 MM patients were included in our study. 71 gemcitabine/cisplatin-treated and 57 pemetrexed/cisplatin-treated MM patients were included in the training groups used to build the respective clinical-pharmacogenetic models. Validation of the gemcitabine/cisplatin model was performed on 66 independent MM patients. Pharmacogenetic scores were assigned by rounding the regression coefficients.

Results: Clinical-pharmacogenetic model predicting outcome of gemcitabine/cisplatin included CRP level, histological type, performance status, *RRM1* rs1042927, *ERCC2* rs13181, *ERCC1* rs3212986, and *XRCC1* rs25487 and had values ranging between 0 and 3.4. Cutoff value of 0.75 had sensitivity of 0.62 and specificity of 0.81. Patients with higher score had shorter progression-free survival (PFS) (P<0.001) and shorter overall survival (OS) (P<0.001). In the validation group, positive predictive value was 0.74 and negative predictive value was 0.56. Clinical-pharmacogenetic model predicting outcome of pemetrexed/cisplatin included CRP level, *MTHFD1* rs2236225, and *ABCC2* rs2273697 with scores ranging between 0 and 3.9. Cutoff value of 2.7 had sensitivity of 0.75 and specificity of 0.61. Patients with higher score had lower probability of good response and shorter PFS (P<0.001).

Conclusions: Clinical-pharmacogenetic models could enable stratification of MM patients based on their probability of response to gemcitabine/cisplatin or pemetrexed/cisplatin and improve treatment outcome. This approach could be used for translation of pharmacogenetic testing to personalization of chemotherapy as a way of selecting the most favorable treatment option for each patient.

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FT-22. The pharmacogenetic model of influence of transporters polymorphisms and clinical factors on methotrexate inefficacy in rheumatoid arthritis patients

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Background: Methotrexate (MTX) is the first line choice for rheumatoid arthritis (RA) treatment, however a considerable proportion of patients fail to achieve an adequate response. Increasing amount of data indicates that several genes and clinical factors influence MTX treatment response. New statistical approaches are needed to analyze large number of covariates in small data sets. Due to greater statistical power and ability to detect smaller effects, lasso penalized regression could be used in building pharmacogenetics models.

Objective: To analyze combined influence of polymorphisms in genes coding for MTX transporters and clinical factors on MTX treatment inefficacy.

Methods: The testing group was comprised of included 102 RA patients from 2007 till 2013 and validation group of 131 patients included before 2007. Clinical data were obtained from the medical records. *ABCB1* rs1128503, *ABCC2* rs2273697, rs2804402, rs717620, *ABCG2* rs2231137, rs22311342 and *SLCO1B1* rs4149056, rs11045879 and rs2306283 polymorphisms were genotyped using allele-specific real time polymerase chain reaction (KASPar, Kbiosciences, Hoddesdon, UK). The combined effects of genetic factors as well as clinical factors were analyzed with lasso penalized regression.

Results: Univariate analysis showed influence of MTX dose (p<0.000; OR=1.08) and *SLCO1B1* rs2306283 (p=0.039, OR=1-23) on MTX inefficacy in testing group, in validation group MTX dose (p<0.000, OR=1.06) and RF or anti-CCP seropositivity (p=0.007, OR=1.31) showed association. In lasso penalized regression model in testing group *ABCB1* rs1045642 (OR=1.48), *SLCO1B1* rs2306283 (OR=1.58), ABCC2 rs2804402 (OR=1.27), erosions (OR=1.12), RF (OR=1.74) and MTX dose (OR=1.44) were significant (model p-value 0.0034). In validation group only RF or anti-CCP seropositivity (OR=1.44) and MTX dose (1.17) showed to be associated (model p-value= 0.003)

Conclusion: With lasso penalized regression we validated the influence of RF and MTX dose on MTX inefficacy.

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FT-23. Guaraná and its main bioactive molecules modulates differentially the *D. melanogaster* transcriptome

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Guaraná (Paullinia cupana) is an Amazon (Brazil) fruit commonly used as energetic beverage due to its high caffeine content. This plant also contains catechins, theobromine, and tannin. Previous investigations suggest a broad diversity of guaraná biological effects affected indicates its potential pharmacogenomics property. However, investigations involving the guaraná effect on genome and metabolome are still incipient. For these studies,

Drosophila can be considered an ideal organism to analyze gene-nutrient interactions because of its small size and well characterized genome, and by the fact, that over 70% of all known human disease genes are present in Drosophila and have conserved functions. Therefore, we analyzed the impact of acute (24h) and moderate (72h) guaraná supplementation on transcriptome of male Drosophila melanogaster, and whether this effect is cause by main compound caffeine and catechin. Five days old flies were fed with glucose/yeast standard medium with or without 10mg/mL guaraná supplementation for a period of 24h and 72h, and medium containing only the main chemical molecules present in guaraná powder at concentrations estimated to be found in 10 mg/g guaraná: total catechins (0.471mg/mL), caffeine (1.33mg/mL) and a combination of total catechins and caffeine. The microarray analysis was commercially performed by Takara Bio Inc. / Japan Company, an Agilent technology certified service provider. Genes from flies treated with guaraná with presented > 2 more intensity signal of untreated control group were considered upregulated, whereas genes with < 0.5 intensity signal of untreated control group were considered downregulated. A total of 648 genes presented a difference of expression levels among all treatments when compared to control group. The genes were split in two groups: biological function known 68.52% (n = 444) and function unknown 31.48% (n = 204). Analysis of genes from first group showed that: in acute effect 71 genes (37 upregulated, 34 downregulated) had their levels change just by guarana. Considering the moderated effect 13.58% of the genes were up or downregulated just by guarana. The influence of caffeine was observed in 7.89% of genes, and 7.65% of the genes were influence by catechin, and around 11.7% genes were influence by catechin + caffeine. Guaraná regulated genes

involving with cellular detoxification, development, immune response and some neurobehavioral response. The preliminary results appoint that guaraná intake has a systemic impact on Drosophila gene regulation. Complementary investigations need to be performed to evaluate the effect of these modulations on fruitfly metabolism.

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FT-24. Towards a pharmacogenomics information system for personalized medicine

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In the post-genomic era, the increasing flow of genetic data emerging from both research and Direct to Consumer (DTC) services triggers the development of informatics tools, systems and databases that urge to cope with the genetic information overload. In the area of pharmacogenomics (PGx) and personalized medicine, along with evolving technologies that enhance data connectivity, emerging information systems should vitally contribute in translating the growing number of genetic variants into clinical aspects and facilitate gene-based drug prescribing. The identification of biomarkers that can predict drug toxicity and response is of primary importance in the PGx field, since it directly supports individualization and rationalization of treatment.

Several pharmacogenomics databases that provide useful information in the aforementioned respect are being developed sporadically [1, 2]. Although current scientific PGx knowledge bases offer quality of information and many of them are freely available (e.g., PharmGKB; www.pharmgkb.org), they are not joined with personalization services, and cannot be updated by the end user. Conversely, the ever-increasing DTC companies that offer personalization services are not publicly available and are not designed to serve research purposes. According to our knowledge, there is no 'one stop' Web-based platform yet, for PGx knowledge recording, processing, assimilation and sharing.

Here, we discuss the design of an integrated electronic PGx Assistant (ePGA) that provides personalized genotype-to-phenotype PGx translation services, linked with respective drug recommendations. The inclusion of a personalized PGx translation component into the ePGA system is founded on the assumption that "clinical high-throughput and pre-emptive genotyping will eventually become common practice and clinicians will increasingly have patients' genotypes available before a prescription is written" [3]. Translation is based on the 'matching' of individual genotype (SNP) profiles against PGx gene haplotypes, and the subsequent inference of the corresponding metabolizer phenotypes. Currently ePGA employs harmonized haplotypes-tables from PharmGKB and DMET™ Plus [4], and it aims to act as a single portal that supports medical professionals and researchers in the identification and documentation of PGx gene variants.

The main functionalities provided by the system are: (i) retrieval of PGx information regarding gene-variants, drugs, and pharmacogenes, i.e., genes enabled in the absorption, distribution, metabolism, excretion and toxicity (ADMET) of drugs; (ii) update and insertion of PGx-related information on newly discovered gene-variants (i.e., the involved haplotypes/alleles linked with the inferred metabolizer phenotype); (iii) matching of (individual) genotype-profiles with gene PGx haplotypes and inference of the respective diplotypes – a special algorithmic process is accommodated for that [5]; and (iv) delivery of respective personalized drug recommendations.

The data-model underlying the system is based on a star-schema organization of data, a very common business model for organizing data that we extended into the PGx domain. The designed star-schema is centered on a fact table that allows the storage of many different kinds of data: genes, gene-variants, haplotypes, diplotypes and alleles, metabolizer phenotypes, as well as drug clinical annotations and recommendations. We employ Django (www.djangoproject.com) as the web-application framework that follows the model–view–controller architectural pattern to implement the proposed ePGA system.

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FT-25. Role of the rs6313 and rs1799978 variants as pharmacogenomic biomarkers in Greek, Italian and Croatian schizophrenia patients

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It is well documented that schizophrenia is the most enigmatic and devastating psychiatric syndrome, that affects both sexes and all ages. Its etiology is still unknown; however, both environmental and genetic factors seem to play important role. Schizophrenia can be treated through the use of antipsychotics but unfortunately, the high rate of 15% of schizophrenics does not respond positively to treatment. Clozapine is the first atypical drug and is usually indicated in treatment-resistance schizophrenia and in patients who are at high risk of committing suicide. Risperidone is also an atypical antipsychotic, effective both in positive and negative symptoms of PANSS scale (Positive and Negative Symptom Scale). We performed a literature review and meta-analysis of various pharmacogenomic biomarkers for the individualization of risperidone and clozapine treatment. Subsequently, we verified our findings in healthy controls and schizophrenia patients of Greek, Italian and Croatian origin. The meta-analysis included 49 studies, 6786 controls and 5705 patients. The sample we used for our experiments contained 20 Greek schizophrenics and 100 Greek controls, 92 Italian schizophrenics and 92 Italian controls as well as 50 Croatian schizophrenics and 50 Croatian controls. The group of patients included two sub-groups, one treated with clozapine and one treated with risperidone. For the genotyping we used a PCR/BpEI-based method and sequencing. Our meta-analysis indicated rs6313 and rs1799978 as potential pharmacogenomic biomarkers for treatment response of schizophrenics to clozapine and risperidone. Our preliminary results, indicated that in case of Greeks, A allele of rs6313 was present at 56% and G at 44% in controls, while in schizophrenics A allele was 56,5% and G 43,5%. As for rs1799978 marker, T allele was 89,5% and C was 10,5% in controls and 94% and 6% in patients, respectively. Italian schizophrenia patients presented the A allele of rs6313 at 56,9% and G at 43,1% in controls, while in schizophrenics A allele was 57% and G 43%. T allele of rs1799978 was present 91,4% and C was 8,6% in controls and 88,2% and 11,8% in patients, respectively. Studying Croatian population we found that A allele of rs6313 was present at 44% and G at 56% in controls, while in schizophrenics A allele was 44,3% and G 55,7%. Considering rs1799978, T allele was 92,5% and C was 7,5% in controls and 90% anod 10% in patients, respectively. Preliminary findings suggest that rs6313 and rs1799978 may not be associated with clozapine and risperidone treatment efficacy in Greek, Italian and Croatian schizophrenics.

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FT-26. Development of a novel tumor homing compound targeting selectively glioblastoma cells

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Introduction: Glioblastoma Multiform (GBM), is considered to be one of the most

fatal types of cancer with a median patient survival of 12 to 15 months. Based on clinical and genetic parameters, GBMs are classified into primary and secondary. Primary, are characterized by EGFR amplification as well as mutations, loss of heterozygosity of 10q, deletion of the phosphatase and tensin homologue on chromosome 10 (PTEN 10), and p16 deletion. Secondary GBMs have transcriptional patterns and aberrations in the DNA copy number that differs significantly from those of primary GBMs. Despite all molecular and genetic differences GBMs have indistinguishable morphology and low success rate in response to conventional therapies, limiting the ability of histopathology in providing a firm prognosis for patient survival. Current therapies include radiotherapy concurrent with temozolamide, while recently FDA approved bevacizumab as adjuvant therapy for patients with progressive GBM. Another therapeutic perspective involves molecularly targeted therapies and a series of clinical trials are performed using TKIs, investigating single or multiple targeting concomitantly. Unfortunately, the majority of therapeutic approaches are so far disappointing, emerging crucially the need for novel more effective treatment agents. In the current project we developed a tumor homing peptide able to selectively kill glioblastoma cells and spare normal cells.

Materials and Methods: Synthesis of the peptide was performed using classical Fmoc- a-aminoacid based synthesis. The novel agent was tested for its effect in both GBM (U87, LN18 and M059K) and non cancerous cells (L-929, MCF-10A). Cell number was estimated using methyl-tetrazolium assay. In addition, several types of cell death were determined including apoptosis (programmed cell death type I), autophagy (programmed cell death type II) and necrosis as well as cell cycle arrest. Annexin V and dead cell assay kit was used for apoptosis and necrosis, western blot with a-beclin-1 for autophagy and a cell cycle assay kit for the distribution of cell cycle phases.

Results and discussion: The EC_{50} of the novel compound was determined in both GBM cells and non cancerous cells L929 & MCF-10A. The anti-proliferative effect was associated with a specific type of cell death.

Conclusions: Herein, we have developed a novel tumor homing peptide that selectively targets glioblastoma cells and is also able to be used as a carrier of biological cargoes and/or cytotoxic agents. In addition, the novel compound could be used as a theranostic agent if combined with an appropriate fluorophore.

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FT-27. Assessment of the *STAT4* rs7574865 SNP in genetic susceptibility of early-onset Myasthenia gravis

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Myasthenia gravis (MG) is a heterogeneous autoimmune disease mediated by the presence of autoantibodies that bind to components of the neuromuscular junction, thus leading to impaired signal transmission over the postsynaptic membrane. Clinically, MG is characterized

by muscular weakness and rapid fatigability, aggravated by exercise and relieved by rest. In 80–85% of MG patients, the muscle acetylcholine receptor (AChR) constitutes the major target, whereas in the rest of the MG patients, pathogenic autoantibodies are directed towards the muscle-specific tyrosine kinase (MuSK) or the low-density lipoprotein receptor-related protein 4 (LRP4). Like most autoimmune disorders, MG is a non-inherited disease and is considered to have a multifactorial underlying basis, with an established contribution of genetic factors, though. The heterogeneity observed in MG perplexes genetic analysis even more, as it occurs in various levels, including diverse autoantigens, thymus histopathology, and age at onset. Several association studies in distinct MG groups, including the first genome-wide association study (GWAS) conducted on a group of North European MG patients, have assessed the involvement of numerous HLA and non-HLA related loci in MG susceptibility. The signal transducer and activator of transcription – 4 (STAT4) is expressed in the lymphoid and myeloid cell lineages and it is phosphorylated in response to IL-12. It has been shown to up-regulate the IFN-γ production and to induce the differentiation of CD4$^+$ T cells toward the proinflammatory Th1 phenotype. STAT4 has been emerged as a potential risk factor for autoimmunity, as it has been clearly linked to several autoimmune diseases, namely Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE). The SNP rs7574865 (T/G) tags a susceptibility haplotype located within the third intron, which generates the strong association signals observed. In the current study, we intend to evaluate the involvement of the STAT4 rs7574865 polymorphism in genetic susceptibility to MG. Our study group consists of 120 sporadic, early-onset (<40 years) MG cases, all of Hellenic descent, positively detected with anti-AChR autoantibodies. A total of 120 ethnically matched, healthy volunteers are enrolled in the study, too. Genotyping of the subjects will be performed using a TaqMan SNP assay for allelic discrimination. In the context of statistical analysis, differences in genotype distribution and allele frequencies between cases and controls will be calculated by χ² analysis.

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POSTER

PRESENTATIONS

PO-01. Molecular Bases of Gilbert's syndrome in Serbian Population and Methods for Molecular Diagnostics

N Kotur [1], M Stojiljkovic [1], N Radlovic [2], B Zukic [1], B Stankovic [1], K Klaassen [1], S Srzentic [1], G Nikcevic [1], P Kalaba [1], Z Lekovic [2], D Ristic [2], V Radlovic [2], S Pavlovic [1]

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Background: Gilbert's syndrome (GS) is a condition characterized by jaundice due to a chronic, non-hemolytic, unconjugated hyperbilirubinemia. This hereditary condition, present in around 10% of population, is caused by deficiency of UDP-glycosyltransferase 1 family, polypeptide A1 (UGT1A1) enzyme. Number of TA repeats in TATA box of UGT1A1 promoter is known to be reversely correlated with UGT1A1 transcription level. Although GS is considered to be a mild condition, its symptoms might be misinterpreted as a more serious liver illness. DNA analysis might represent a reliable alternative for conformation of Gilbert's syndrome. Furthermore, UGT1A1 enzyme metabolize irinotecan, an anticancer drug, so UGT1A1 testing is recommended prior to the drug administration in order to avoid toxicity.

Objective: Our goal was to validate number of TA repeats in TATA box of UGT1A1 gene's promoter as molecular marker of Gilbert's syndrome in Serbian population and to determine genotypes frequencies. Also, we aimed to compare two molecular methods for detection of the number the TA repeats in the promoter of UGT1A1 gene.

Methods: Blood samples were collected from 54 patients with GS, diagnosed at The University Children's Hospital in Belgrade. Control group consisted of 64 individuals. All subjects were of Serbian origin. After PCR amplification of the promoter of UGT1A1 gene, PCR fragments were analyzed by both, polyacrylamide gel electrophoresis and fragment analysis. Fisher's exact test was applied for statistical analysis.

Results: Both methods, polyacrylamide gel electrophoresis and fragment analysis yielded the same result for every subject tested. A statistically significant difference in genotype frequencies between patients and control group was found ($p < 10^{-10}$). In GS patients, genotype frequencies regarding number of repeats were 7.4%, 16.7%, 72.2% and 3.7% for 6/6, 6/7, 7/7 and 7/8 genotypes, respectively. In control group genotype frequencies were 39.1%, 45.3%, 15.6% and 0%, respectively.

Conclusion: Number of TA repeats in the promoter of UGT1A1 gene is a molecular marker for Gilbert's syndrome in Serbian population. Molecular methods used for detection of the number TA repeats can be considered accurate. The sensitivity of molecular testing for Gilbert's syndrome is about 76% for Serbian population.

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PO-02. Novel transcription regulators in non-coding regions of PAH gene as a step toward personalized medicine

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Phenylketonuria (PKU) is caused by mutations in phenylalanine hydroxylase gene (PAH). Although PAH genotype remains the main determinant, phenotype cannot always be predicted precisely. Previously, we found a transcription enhancer in PAH intron 8 that could affect genotype-phenotype correlation. In this study, we analyzed additional non-coding PAH gene variants.

In silico prediction for transcription factor binding sites pointed to a promoter variant (PAH:c.-170delC) and VNTR variants in 3' region. We transiently transfected HepG2 cell line with various CAT reporter constructs to determine the effect of PAH gene non-coding sequences on transcription. Construct with binding site in promoter and constructs with VNTR3, VNTR7 and VNTR8 had a 50-60% reduction of CAT activity compared to pBLCAT5. EMSA supershift showed binding of KLF1 transcription factor to the analyzed promoter sequence, and binding of C/EBPalpha to VNTR3.

Our study pointed to new elements that could act as transcription silencers and thus influence genotype-based prediction of PKU severity. New transcription regulators will contribute to better understanding of PKU complexity and lead toward personalized medicine.

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PO-03. HLA-DQ Haplotypes in Serbian Pediatric Celiac Disease Patients and Association with Lactase Deficiency

B Stanković [1], N Kotur [1], S Srzentić [1], K Klaassen [1], N Radlović [2], Z Leković [2], D Ristić [2], V Radlović [2], G Nikčević [1], T Kostić [1], S Pavlović [1], B Zukić [1]

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Celiac disease (CD) is a chronic inflammatory disease in small intestine triggered by gluten uptake with strong genetic background. In 90-95% of CD patients HLA-DQA1*05 and DQB1*02 alleles are found, whereas most of the remaining patients carry HLA-DQA1*03 and DQB1*03:02 alleles. Specific HLA-DQ haplotypes define different risk for CD incidence. In CD patients, lactose intolerance could be caused by mucosal damage, or could be inherited. A genetic variants C/T-13910 upstream of the lactase-phlorizin hydrolase (LPH) gene has been strongly associated with lactase deficiency/persistence. Here we presented for the first time the association of HLA-DQ haplotypes with CD in Serbian pediatric patients and estimated risk for CD development that these haplotypes confer. Also, we evaluated association of C/T-13910 LPH gene variants with CD.

A total of 73 CD patients and 62 healthy individuals underwent genotyping for DQA1, DQB1 and DRB1 alleles, using SSP-PCR method. Analysis for C/T-13910 LPH variants were performed using a PCR-RFLP method. In our study, combined presence of HLA-DQA1*05 and DQB1*02 alleles showed strong association with CD (p=9x10-18). The highest risk for CD development was estimated for DRB1*03-DQA1*05-DQB1*02 homozygous haplotype carriers, followed by the risk for carriers of DRB1*03-DQA1*05-DQB1*02/DRB1*X-

DQA1*X-DQB1*02 haplotypes. However, significant differences in the frequencies of analyzed LPH gene variants between CD patients and controls were not found. HLA genotyping proved to be a useful diagnostic tool in estimating risk for CD development. The C/T-13910 LPH gene variants, responsible for inherited lactase deficiency/persistence, were not associated with CD in Serbian pediatric patients.

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PO-04. Wnt signaling blockage by quercetin reduced pluripotency, migration and adhesion of human teratocarcinoma cell line NT2/D1

M Mojsin, J Marjanovic Vicentic, M Schwirtlich, V Topalovic, A Klajn, N Kovacevic Grujicic, D Drakulic, S Davidovic, M Stevanovic

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Quercetin is bioflavonoid widely distributed in fruits, vegetables and plant based food products. Anti-cancer activity of quercetin has been well documented in various types of animal cancer models and cancer cell lines. The Wnt/β-catenin signaling is evolutionarily conserved pathway that regulates crucial steps during embryonic development. Deregulation of this pathway underlies a wide range of cancer pathologies in humans, including pathogenesis of testicular carcinoma

In order to examine therapeutic potential of quercetin in teratocarcinoma, we used human teratocarcinoma cell line NT2/D1 as in vitro model system. We found that quercetin inhibits proliferation, adhesion and migration of NT2/D1 cells and downregulates the expression of pluripotency maintenance factors SOX2, Oct4 and Nanog.

We further showed that quercetin antagonized Wnt/β-catenin signaling pathway in NT2/D1 cells by inhibition of β-catenin nuclear translocation and consequent downregulation of β-catenin dependent transcription. Obtain results suggest that quercetin, as a potent inhibitor of Wnt signaling, possess promising chemopreventive and chemotherapeutic properties for tretman of cancers with aberrant activation of Wnt pathway.

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PO-05. Expression profile of SOXB1 during retinoic acid induced neural differentiation of embryonal carcinoma NT2/D1 cells

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The SOX/Sox family members, divided into 10 distinct groups designated from A to J, are transcription factors which function as regulators of cell fate decisions during development. SOXB/SoxB group members (SOXB1 and SOXB2 genes) play an important role in neural development. The SoxB1 genes, Sox1, Sox2 and Sox3 are panneurally expressed and have redundant role in maintaining the broad developmental potential and identity of neural stem cells. Their inhibition in the

vertebrate embryo leads to premature differentiation of neural precursors while their overexpression is accompanied by inhibition of neurogenesis.

The aim of our study was to determine expression profile of SOXB1 during neural differentiation of pluripotent embryonal carcinoma NT2/D1 cells. The exit from pluripotency of NT2/D1 cells was confirmed by detection of diminished expression of the pluripotency marker OCT4 while neural differentiation was confirmed by induction of the presynaptic plasma membrane protein SNAP25, neuron specific enolase, vimentin, doublecortin, hASH1 and synaptophysin at the final phase of RA induction. We detected dynamic changes in SOXB1 expression during retinoic acid induction. SOX1 protein level was fluctuated during NT2/D1 retinoic acid induction with tendency of decreasing at 3 and 4 weeks of treatment. SOX2 protein was gradually upregulated and its expression remained increased compared to untreated NT2/D1 cells. The SOX3 expression was transiently upregulated after one week of retinoic acid induction, but then gradually downregulated up to 4 weeks of RA treatment. Results obtained by this study signify dramatic changes in SOXB1 proteins level during neural differentiation and indicate that SOXB1 are coexpressed during neural differentiation.

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PO-06. National Genetic databases: The Moroccan example

I Ratbi [1,2], S Chafai Elalaoui [2], ICherkaoui Jaouad [2], P Papadopoulos [3], E Viennas [4], G Tzimas [4,5], J Lyahyai [1], G P Patrinos [6], A Sefiani [1,2]

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The exponential discovery rate of new genomic alterations, leading to inherited disorders, as well as the need for comparative studies of different populations mutation frequencies necessitates recording their population-wide spectrum, in online mutation databases. The National Mutation Databases are continuously updated mutation depositories, which contain extensive information over the described genetic heterogeneity of an ethnic group or population. We have previously developed the Moroccan Human Mutation database (http://www.sante.gov.ma/Departements/INH/MoHuMuDa/index.htm) to document the incidence of genetic disorders in the Moroccan population. Here, we report the upgrade of the Moroccan Human Mutation database (http://ethnos.findbase.org/home-ma) using the upgraded version of the ETHNOS software, developed by the Golden Helix Institute of Biomedical Research. The upgraded version of the ETHNOS software expands the previous querying capacity and provides new visualization tools, based on PivotViewer and Microsoft Silverlight technology, to comprehensively query and retrieve the data documented in the

database, namely 171 disease summaries and 318 mutation frequencies, where possible. In the latter case, mutation frequency data have been made available using bidirectional links from the Frequency of Inherited Disorders database (www.findbase.org; van Baal et al., 2007; Georgitsi et al., 2011). Furthermore, there are numerous links to the respective Online Mendelian Inheritance in Man (OMIM) entries and, when available, to the locus-specific databases fruitfully integrate the databases content into a single web site. The Moroccan Human Mutation database, especially in its present format, can serve as a valuable online tool for molecular genetic testing of inherited disorders in the Moroccan population and could potentially motivate further investigations of yet unknown genetic diseases in this population.

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PO-07. Influence of gene variants and expression level of inflammatory mediators on occurrence of Perthes disease

S Srzentic [1], V Spasovski [1], D Spasovski [2, 3], Z Zivkovic [4], D Matanovic [2,5], Z Bascarevic [2,3], Z Terzic Supic [2], M Stojiljkovic [1], T Karan-Djurasevic [1], B Stankovic [1], S Pavlovic [1], G Nikcevic [1], Z Vukasinovic [2, 3]

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Perthes disease is idiopathic avascular osteonecrosis of the hip in children, with unknown etiology. Inflammation is present during development of Perthes disease and it is known that this process influences bone remodeling. Since genetic studies related to inflammation haven't been performed in Perthes disease so far, the aim of this study was to analyze the association of frequencies of genetic variants of immune response genes: toll-like receptor 4 (TLR4), tumor necrosis factor alpha (TNF-α), interleukin-3 (IL-3) and interleukin-6 (IL-6), as well as the level of IL-6 gene expression, with this disease.

The study cohort consisted of 37 patients with Perthes disease and 50 healthy controls from Serbia. Polymorphisms of TLR4 (Asp299Gly, Thr399Ile), TNF-α (G-308A) and IL-6 (G-597A, G-174C) genes were determined by polymerase chain reaction restriction fragment length polymorphism method, while IL-3 gene polymorphisms (C-16T, C132T) were determined by direct sequencing of PCR product. Expression level of IL-6 gene was determined by qRT-PCR method.

TLR4 polymorphisms (Asp299Gly, Thr399Ile) were in complete, while IL-3 (C-16T, C132T), as well as IL-6 (G-597A, G-174C) polymorphisms were in perfect linkage disequilibrium. A statistically significant increase of heterozygote subjects for IL-6 G-174C/G-597A variants was found in controls in comparison to Perthes patient group (P=0.047, OR=2.49, 95% CI=1.00-6.21). Also, the patient group for IL-6 G-174C/G-597A variants wasn't in Hardy-Weinberg equilibrium. No statistically significant differences were found between patient and control groups

for TLR4, TNF-α and IL-3 analyzed variants, nor for the IL-6 expression level.

Our results suggest that children who are heterozygous for the IL-6 G-174C/G-597A polymorphisms have a lower chance of developing Perthes disease than carriers of both homozygote genotypes.

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PO-08. Comparative study and meta-analysis of meta-analysis studies for the correlation of genomic markers with early cancer detection

Z Lanara [1,2], E Giannopoulou [3], M Fullen [4], E Kostantinopoulos [2], J-C Nebel [4], H P Kalofonos [3], G P Patrinos [2], C Pavlidis [2]

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Introduction: 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 (1) among genes which when mutated lead to different types of cancer (e.g.common metabolic pathways) and (2) between groups of genes and types of cancer.

Methods: We have meta-analysed 150 meta-analysis articles which included 4,474 studies, 2,452,510 cases and 3,091,626 controls (5,544,136 individuals in total) including various racial groups and other population groups (native Americans, Latinos, Aborigines, etc.). Three types of studies were included: (1) pooled analysis, (2) GWAS and (3) other studies, e.g. search in published reports. Data were processed using a state-of-the-art general purpose clustering tool, CLUTO.)The biological significance of those clusters was first, evaluated using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING).

Results: Our results were not only consistent with previously published literature but also depicted novel correlations of genes with new cancer types. Our analysis revealed a total of 17 gene-disease pairs that are affected and generated gene/disease clusters, many of which proved to be independent of the criteria used, which suggests that these clusters are biologically meaningful.

Conclusion: Our meta-analysis study generated clusters of genes and diseases, many of which proved to be independent of the criteria used, which suggests that these clusters are most likely biologically meaningful . Preliminary study of some clusters and of our results shows that indeed these genes interact. As regards the associations, with further literature analysis on human and mouse models, we

have also found meaningful gene associations related to other cancer types not previously reported in the literature, and observation that warrants further investigation.

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PO-09. Molecular genetic characteristics of hyperphenylalaninemias in Serbia and implications for personalized medicine

M Stojiljkovic [1], K Klaassen [1], M Djordjevic [2], A Sarajlija [2], B Kecman [2], A Skakic [1], M Ugrin [1], B Zukic [1], G Nikcevic [1], S Pavlovic [1]

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Hyperphenylalaninemias (HPA), namely phenylketonuria (PKU) and tetrahydrobiopterin (BH4) deficiencies, are rare inborn metabolic diseases. For years, PKU patients were treated only with low phenylalanine diet and BH4-deficiencies patients with BH4-supplementation therapy. Recently, it was observed that pharmacological doses of BH4 can lower blood phenylalanine concentration in PKU patients as well.

To date, we have performed genetic analysis of 62 HPA patients from Serbia. By combining DGGE and DNA sequencing, we identified mutations in PAH gene of 61 patients (98%) and in PTS gene of 1 patient (2%). We identified 26 different mutations in PAH gene, among them 8 BH4 therapy responsive (52.6% overall relative frequency). In PTS gene, we identified only p.D136V.

For countries like Serbia, where BH4 differentiation test isn't available, we propose prompt genetic analysis of PAH gene in order to target rare patients with possible BH4 deficiency. Furthermore, for PKU patients, genotype-based prediction of BH4 therapy responsiveness could point to additional treatment option. Thus, for all HPA patients, genetic analyses will enable personalized treatment and lead to better disease outcome.

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PO-10. Impact of CYP2C19 gene variants on clopidogrel therapy in Serbian patients

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It has been established that CYP2C19 gene variants influence patient response to antiplatelet drug clopidogrel. We investigated the impact of -806C>T and -889T>G variants of CYP2C19 gene on bleeding events in 100 patients taking clopidogrel. Genotyping for -806C>T and -889T>G was performed by direct DNA sequencing. All in hospital bleeding events were assessed using standard medical criteria (BARC and TIMI). In this study we observed significant association between -889T>G variant and TIMI bleeding, but there was no association between -806C>T and any bad clinical outcomes. We recommend further studies to be focused

on possible ways of influence of -889T>G on CYP2C19 expression.

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PO-11. A novel *POP1* mutation discovered in a Moroccan boy with anauxetic dysplasia

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Background: The cartilage-hair hypoplasia – anauxetic dysplasia (CHH-AD) spectrum disorders includes metaphyseal dysplasia without hypotrichosis (MDWH), Cartilage-hair hypoplasia (CHH), and Anauxetic dysplasia (AD). CHH-AD spectrum disorders are characterized by severe disproportionate short stature which is usually recognized in the newborn, joint hypermobility and often fine silky hair. The most severe phenotype is anauxetic dysplasia(AD), which has the most pronounced skeletal phenotype, and may be associated with atlantoaxial subluxation in the newborn. AD is inherited as an autosomal recessive manner, and is caused by mutations in RMRP gene, an untranslated intronless gene, mutations of which also cause cartilage-hair hypoplasia (CHH, OMIM 250250), another severe form of dwarfism. Recently, exome sequencing for a family with two affected daughters with AD showed that POP1 mutation was involved in AD. The patients had a compound heterozygous mutation (c.1573C>T; c.1748G>A) in the *POP1* gene.

Case report: We report a 3 years old boy, consanguineous, unique of his family, addressed for severe short stature, neonatal onset. The clinical and radiographic features of the patient showed anauxetic dysplasia. Sanger sequencing of the entire coding sequence of RMRP and *POP1* genes were performed. RMRP sequencing was normal. POP1 sequencing identified a novel homozygous mutation c.1744C>T; in the exon 13. PolyPhen-2 and SIFT web-based platforms revealed that the mutation was pathological. Our finding confirmed that POP1 gene is involved in anauxetic dysplasia. Importantly, the mutation detected in this study was located few bases before the already reported mutation. Thus, the exon 13 is a hot spot of mutations in the anauxetic dysplasia.

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PO-12. Association of variants in *FTO*, *FABP2*, *PPARG*, *ADRB2* and *ADRB3* genes with obesity in Serbian population: A prerequisite for nutrigenetic algorithm development

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Obesity has become a major health problem worldwide. It is a result of interaction between environmental, behavioral, socio-economic factors and

genetics, but the molecular mechanisms of its development has not yet been clarified. Several studies have reported an association between single nucleotide variants in the FTO (rs9939609), FABP2 (p.A54T), PPARG (p.P12A), ADRB2 (p.R16G and p.Q27E) and ADRB3 (p.R64W) genes and obesity. However, this association has never been studied in Serbian population. In this study we analysed presence of six afore-mentioned variants in 70 individuals (30 normal-weight, 40 overweight) from Serbian population by using PCR-ARMS, PCR-RFLP and DNA sequencing. Allelic frequencies of variants rs9939609, p.A54T, p.P12A, p.R16G, p.Q27E and p.R64W were 55.0%, 67.5%, 82.5%, 58.8%, 73.8% and 87.5% respectively. Frequency of majority of variants was similar to various Caucasian populations, except for p.A54T variant which had notably higher frequency in Serbian population. Based on these preliminary results, selected variants will be included in development of nutrigenetic algorithm, needed for planning of individualized nutrition based on genetic predisposition.

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PO-13. Awareness of private and public high school students about genetics and nutrigenomics in Greece

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Nutrigenomics is an emerging discipline which aims to investigate how a person's individual genetic composition correlates with their dietary intake and explores how nutrition influences gene expression. To this end, nutrigenomics attempts to integrate three main –omics technologies, namely metabolomics, transcriptomics and proteomics. For the purposes of this study, we collected 375 questionnaires from both private and public high schools in Greece in order to evaluate the views and knowledge of students on genetics and nutrigenomics. We used the SPSS 18.0 statistical package in order to perform the statistical analysis. The vast majority of high school student groups were aware of the existence of DNA (97.5% and 97.1% for the public and the private schools, respectively) and the genetic material (90.6% and 93.2% for the public and the private schools, respectively; p=0.032). Almost two thirds of the respondents (68.8% for the public and 62.4% for the private school) were of the view that their body weight was related to their genes. More than 70% of the entire sample (76.1% public school, 77.2% private school students) considered there to be a relationship between obesity and one's genes. We conclude that more information is required by all age groups on genetic testing in general and in nutrigenomics' testing in particular. The prescription of nutrigenomics testing by both a doctor and dietitian was stated as the preferred scenario by the participants of both nutrigenomics studies, emphasizing the fact that healthcare professionals should interpret the results from a genetic test to the interested individuals/patients. Overall, nutrigenomics holds out considerable promise for both the optimization of health and nutrition and

lowering healthcare costs, provided of course that many ethical questions are addressed prior to full implementation of nutrigenomics in mainstream medical practice.

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PO-14. MDM2 SNP 344T/A polymorphism in breast cancer chemotherapy

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The breast cancer is the most frequent cancers of the women in the world, its incidence is increasing but the mortality has decreased in a considerable way, thanks to the progress of the various anticancer treatments. The protocols of anticancer chemotherapy containing anthracyclines are in indisputable progress in oncology. The resistance to anthracyclines represents the major factor limiting their use. Several oncogene products or tumor suppressor proteins which are involved in the apoptotic pathway have been suggested to be involved in chemotherapy resistance mechanisms, because induction of apoptosis has been considered to be central to the efficacy of anticancer treatments, for example in breast cancer, overexpression of MDM2 protein prevent the accumulation of activated P53 that's lead the tumor cell to resist to chemotherapy. These data suggest that MDM2 plays in important role in chemoresistance. This study investigated the association of MDM2 polymorphism with the chemoresistance in breast cancer.

To document the role of MDM2 polymorphism, SNP344 T/A(rs1196333) in chemoresistance, in breast cancer, a study was realized in 400 patients with invasive ductal carcinoma (IDC), treated with anthracyclines. The extraction of DNA was performed using the phenol-chloroform method. Anthracyclines Response was scored according to the World Health Organization (WHO). Genotyping was done by the Real Time PCR « Taqman » (Assay ID C__7469117_10) method. Data were statistically analyzed using X2 test. The analysis of the clinical data revealed that median age was 48 years old and 48% of patients were menopausal. Median tumour size was 6 cm and 80% of patients had clinical lymph node involvement. The pathological and laboratory characteristics of the tumours were as follows : 90% of tumours were grade 2 or 3, progesterone receptors (PR) were positive in 52% of patients, and oestrogen receptors (ER) were positive in 57% of patients. 24% of patients presented tumour progression. The analysis of genetic data revealed that among 400 patients with (IDC), we observed the SNP344T-variant in 365 individuals (91%) in which 84 are resistant to chemotherapy, and the SNP344A-variant in 35 individuals (9%) in which only 11 are resistant to chemotherapy. So the resistance to chemotherapy does not seem to be correlated with polymorphism SNP 344 T/A in our population. Indeed, as this polymorphism is located on the SNP309T allele, it'll be suitable to confirm our data, studying both variations.

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PO-15. Toxicogenetic effect of Ala16Val-SOD2 polymorphism in methyl mercury exposition

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Introduction: Worldwide spread, methyl mercury (MeHg) is a well-known threat to human health owing to its capacity to cause systemic toxicity. The process responsible for triggering MeHg toxicity is incompletely understood and likely involves metabolic alterations such as increased oxidative stress and inflammatory response, which in turn can be modulated by many different polymorphisms. Nevertheless, gene polymorphism studies related to oxidative stress triggered by Hg intoxication metabolism have focused mainly on glutathione-related enzymes. However, to define genetically susceptible risk groups, research is also needed on other toxicity pathways. Of particular interest is the manganese SOD enzyme (MnSOD), a primary antioxidant enzyme in the mitochondria that converts superoxide anion into oxygen and hydrogen peroxide (H_2O_2). The human MnSOD gene displays a diallelic polymorphism in the mitochondrial targeting sequence (MTS) in which alanine 16 (GCT) is replaced by a valine (GTT) (Ala16Val MnSOD polymorphism) resulting in 3 genotypes (AA, VV and AV) that impact in the enzyme structure and catalytic efficiency. We showed that this polymorphism can modulate MeHg toxicity due to its capacity of product different amounts of H_2O_2 related to genotype (AA > AV > VV) whereas VV presented a higher cellular viability when exposed to 2,5µM MeHg

(Algarve et al., 2013). But how many folds are the lethal doses between the Ala16Val-SOD2 genotypes? Methods: To test MeHg cytotoxicity in human peripheral blood mononuclear cells (PBMC) of carriers previously genotyped with different Ala16Val genotypes, we performed cell culture with and without MeHg (0; 0,1; 0,3; 1; 3; 10µM) during 24h at 37°C in a humidified atmosphere. After this period, we analyzed cell viability and free DNA in culture medium throug h MTT and PicoGreen (PG) assays. Results and Discussion: Preliminary data suggest that the difference is 1,43 fold higher MeHg concentration in VV genotype than AA, it means that to kill 50% of VV's PBMC is necessary 11,31µM when to kill the same ratio in AA genotype is necessary 7,9µM MeHg.

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PO-16. Uridine-Glucuronosyltransferases 2B15 and 2B17 gene polymorphisms and breast cancer in Tunisian women

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Introduction: Breast exposure to high steroid levels for a long period represents a major risk factor of breast cancer. In fact, elevated estrogen levels in breast tissue may be the result of an increased biosynthesis, or a reduced catabolism of the hormone or its precursors.

Objective: To study the Uridines Glucuronosyltransferases (UGT) genes UGT2B15 and UGT2B17 polymorphism implication in breast cancer in Tunisian women.

Materials and Methods: One hundred ninety seven patients with breast cancer and 176 healthy Tunisian women were included. DNA was extracted from leucocytes, amplified by nested AS-PCR for UGT2B15 polymorphism (Asp85Tyr) and by multiplex PCR for *UGT2B17* gene deletion, and then analyzed by agarose gel electrophoresis. Statistical analysis consisted on Khi2 test with 5% threshold.

Results: Homozygous deletion of UGT2B17 gene was significantly more present in healthy women than in patients (30.28% vs 18.13%; OR=0.51, p=0.006). Absence of UGT2B17 would have a protective role in breast cancer. This role is more settled by stratifying the studied population depending in menopausal status and menarche age. However, no correlation was observed between *UGT2B15* D85Y polymorphism and breast cancer.

Conclusion: To our knowledge, this is the first study of UGT gene polymorphism and breast cancer in Tunisian women. Our results suggest a protective role of *UGT2B17* deletion in breast cancer.

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PO-17. A pharmacogenomics dashboard of 1000 genomes project populations

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The last decade has witnessed significant advances in Pharmacogenetics and Pharmacogenomics (PGx), which holds promise to personalize medical interventions by determining genetic influence in drug response and therefore enabling tailor-made drug prescription according to an individual's genetic makeup. Identifying gene-variants responsible for drug response could also help understand the genetic architecture underlying drug absorption, distribution, metabolism, excretion and toxicity (ADMET).

The 1000 Genomes Project (1kG) is an international research effort that aims to provide the most comprehensive map of human genetic variation using next-generation sequencing platforms. The availability of extensive genotype data from the 1kG has opened the floodgates to researchers to study human genetic variation in several research areas, including pharmacogenomics.

In this work, we utilize methods and tools developed during the design and implementation of an electronic PGx Assistant (ePGA). In particular, we rely on the PGx translation component of ePGA, which is based on the 'matching' of individual genotype (SNP) profiles against PGx gene haplotypes, and the subsequent inference of the corresponding metabolizer phenotypes (currently ePGA employs gene haplotypes-tables from PharmGKB (www.pharmgkb.org) .We applied the translation methodology on the 1kG 1,092 samples, which are distributed among fourteen different populations. We focus on 69 core pharmacogenes, i.e., genes directly related to the ADMET of drugs (about 200 drugs), and target 500 SNP biomarkers being located in these genes and involved

in the haplotype-tables. By analyzing these 500 SNP biomarkers we assigned a PGx gene-specific metabolizer profile (phenotype) to every individual sample.

Our analysis shows that PGx metabolizer profiles differ significantly among 1kG populations in most (~75%) of the studied pharmacogenes. The most significant PGx profile variation among 1kG populations was found in CYP4A22 and is attributed mainly to the Poor_or_Ultra_rapid Metabolizer profile (PUM) of Luhya in Webuye, Kenya (LWK) population [χ^2(18, N=202)=208,35, p<0.00005], in contrast to the Extensive Metabolizer (EM) profile in which the majority of all other populations belong. For the BRCA1 gene, PUM profiles of African ancestry population, and EM profiles of Asian ancestry population exhibit a significant pattern variation [χ^2 (26, N=553) =510, 80, p<0.00005]. All Asian (CHB, CHS, JPT) and African (ASW, LWK, YRI) populations contribute to the significance of PGx variation in PIK3CA, however their PGx profile contribution is complementary [χ^2 (26, N=1092) = 469, 07, p<0.00005]. In general, individuals of African ancestry exhibit greater PGx profile variation in most genes among populations, which can be attributed to their increased genetic heterogeneity.

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PO-18. Resistance to hormone therapy, alters the gene expression pattern in breast cancer cells

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Introduction: Breast cancer is the most frequent malignancy in women. It is estimated that approximately 75% of breast tumors are estrogen receptor positive (ER+) and their growth is stimulated by estrogens. Estrogen-based therapies represent the mainstay in the treatment of hormone-depended breast cancer. Tamoxifen and Fulvestrant belong to routine therapy of ER+ breast cancer patients. Although the estrogen-based therapies have changed the history of hormone-dependent breast cancer, many tumors develop drug resistance. Previous studies have shown that the acquired resistance to Tam in breast cancer cells is accompanied to Src kinase activity elevation. Although similar results for Fulv do not exist, indirect evidences showed that Src inhibition enhanced the antiproliferative effect of Fulv in breast cancer cell line. Furthermore, Src interacts with several RTKs such as EGFR, PDGFR, CSF-1R, IGF-1R, HER-2 and c-Kit. Src interacts with RTKs with a complex and bidirectional way: is a mediator protein after RTK activation as well as modulates the function of RTKs.

Aim: Previous data from our group show that although the treatment of MCF-7 and T47D cells with Fulv and Tam decreased cell proliferation, rendered cells more aggressive regarding cell migration with a possible implication of FAK-Src complex. Based on these data, we developed clones of breast cancer cell line MCF-7 resistant to Tam and Fulv named hereafter MCF-7/Fulv, MCF-7/Tam in order to study changes in gene expression of ERa, EGFR and HER-2 as well as their migration potential.

Materials and Methods: We created cell lines resistant to Fulvestrant (MCF-7/Fulv) and Tamoxifen (MCF-7/Tam). MTT assay was performed to evaluate EC_{50} of cells before and after treatment with endocrine therapy. In addition, real time PCR was performed to estimate the gene expression status of ERa, EGFR and HER-2. Scratch-wound assay was performed in order to estimate collective cell migration.

Results and Discussion: As far as EC_{50} value is concerned, both MCF-7/Fulv and MCF-7/Tam showed increased EC_{50} compared to MCF-7, reassuring the clones' resistance. Resistance to endocrine therapy rendered both clones more aggressive regarding cell migration. Furthermore, gene expression of ERa, EGFR and HER-2 is altered in both resistant clones, demonstrating higher expression in MCF-7/Fulv and lower expression in MCF-7/Tam compared to control. Although both clones have acquired resistance to endocrine therapy, the gene expression pattern of three important genes differs between the two clones. This might occur due to the fact that different molecular mechanisms are involved and merit further investigation.

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PO-19. Correlation between *NOSI* and *ARG2* genomic variants and HbF levels in β-thalassemia major patients

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Hemoglobinopathies result from genetic abnormalities (both quantitative and qualitative) in the hemoglobin molecule production. During the fetal stage, fetal hemoglobin (HbF) production is expressed at high levels, whereas it gradually declines afterwards reaching less than 2% of total hemoglobin shortly after birth. In the clinic, HbF high levels upon hydroxyurea (HU) treatment improve the clinical symptoms of β-thalassemia patients. Various genetic factors have been reported to influence HbF levels in beta-thalassemia, including several SNPs in genes that are linked or not to the human globin cluster. Herein, we focus on the genetic variants of the *NOSI* (rs7977109) and *ARG2* (rs10483801 and rs 10483802) genes that are involved in nitric oxide production and notably, have been associated to HbF increase. For this, an ARMS-PCR methodology has been developed and employed. Genomic DNA was isolated from blood, obtained with informed consent from 90 β-thalassemia major patients and equal number of non-thalassemic individuals of Hellenic origin. Our preliminary findings indicate that there is no statistically significant difference for the genetic variants investigated, between β-thalassemia major patients and healthy individuals. Further investigation is currently on going to investigate the incidence of these variants in β-thalassemia intermedia patients.

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PO-20. Pharmacogenomics and public health in the Hellenic population

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So far, the pharmacogenomic studies in the Greek population have been extremely limited. Hence, the only genetic variants to be studied today that may result in candidate pharmacogenomic markers are coming from studies in individuals of European descent (CEU). In this study, we aim to investigate in depth pharmaco-genomic markers in the Greek population and determine their frequencies. Then, the latter will be compared to the HapMap of the CEU population. For this, we studied 1936 pharmacogenomic markers in 231 genes of interest in 50 healthy individuals of Greek origin, using the DMET+ microarray (Affymetrix, Santa Clara, CA, USA). Following an extensive statistical analysis, 46 pharmacogenomic markers were obtained, showing a statistically significant deviation between the two populations, namely Hellenic and CEU (p<0.05). These pharmacogenomic markers are currently being investigated in a larger sample size, to be exploited in the rationalization of the current therapeutic approaches in Greece. In this way, the public health system will be favored to a great extent, since a better therapeutic outcome will be obtained, avoiding possible toxicities at a lower cost.

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PO-21. Identification of a peripheral blood transcriptional biomarker panel associated with post–myocardial infarction heart failure

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Heart failure (HF) is the most common cause of morbidity and mortality in the developed countries, especially considering the demographic tendencies in their populations. The development of HF after acute myocardial infarction (AMI) is a result of left ventricular (LV) remodeling. This complex process, which is strongly associated with adverse outcome, involves changes in cardiac morphology affecting both cellular and extracellular elements of the myocardium. Early prediction of LV remodeling and development of HF after AMI is a challenge and may potentially be improved by the identification of novel molecular biomarkers associated with this process.

In our study we identify biologically relevant transcripts that are significantly altered upon HF and are associated with its progression. Blood samples were collected from n = 111 patients with AMI and from n = 41 patients from a validation cohort. The patients underwent comprehensive clinical evaluation on admission and throughout the follow-up period of six months. Total RNA isolated from peripheral blood mononuclear cells (PBMCs) was used for microarray analysis (Affymetrix Human Gene 1.0 ST microarrays). We obtained transcription signatures soon after AMI and throughout the follow-up, and found that in the acute phase of AMI dozens of genes from several pathways linked to lipid/glucose metabolism, platelet function and atherosclerotic plaque stability showed altered expression in PBMCs. On the basis of plasma NT-proBNP and ejection fraction, the AMI patients were divided into quartile groups. We have

identified a set of genes whose expression differed significantly between HF vs. non-HF patients on the 1st day of AMI. Validation by RT-qPCR was carried out for selected genes expressed significantly differently between HF vs. non-HF patients on admission: FMN1 (Formin 1), TIMP1 (Metalloproteinase inhibitor 1), RNASE1 (Ribonuclease, RNase A family, 1), JDP2 (Jun dimerization protein 2). Additionally, the analyses were performed on the validation cohort and these results confirmed the prognostic value of the chosen genes. In summary, the identified changes in gene expression over time that differentiated HF patients from non-HF ones may serve as a novel tool contributing to prognosis and diagnosis of HF.

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