LSHB-CT-2006-018822

DANUBIOBANK

The Danubian Biobank Initiative: Towards Information-Based Medicine

Instrument: Specific Support Action
Thematic Priority: FP6-2004-LIFESCIHEALTH-5; LSH-2004-1.1.0-3
Life Sciences, Genomics and Biotechnology for Health

THE DANUBIAN BIOBANK INITIATIVE: TOWARDS INFORMATION-BASED MEDICINE

Publishable Final Activity Report

Final Report 2006-2008

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Start date of the project: 01.01.2006 Duration: 36 months

Project coordinator name: Prof. Gerd Schmitz

Project coordinator organisation name: University of Regensburg

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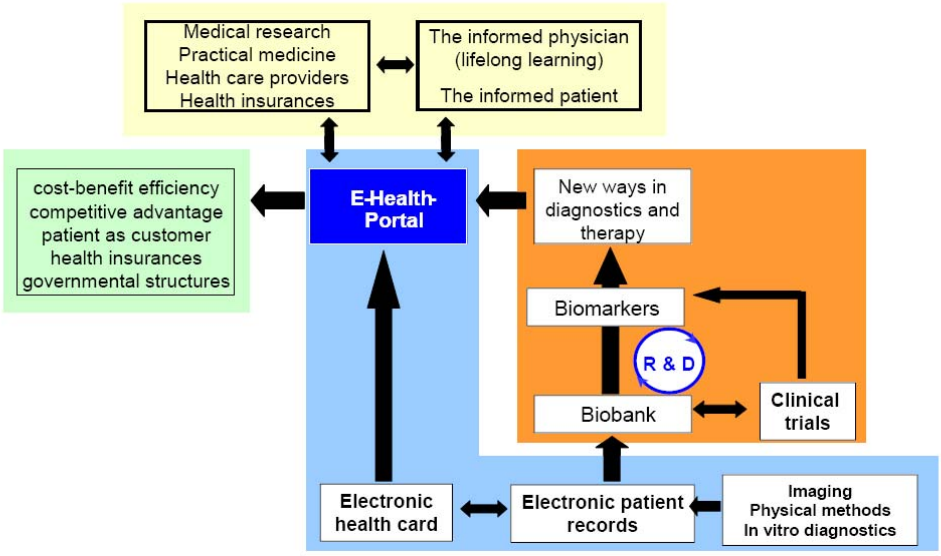
1. Project Execution

The presence of aging disorders in the fast growing population group of over 65 years in the European population presents a challenge for public health care systems in Europe. A key element in coping with this process is the availability of well classified, large enough patient cohorts and the establishment of quality-controlled central banks for DNA, serum, plasma, and cells/tissues/RNA/proteins together with the development of an IT based infrastructure to provide samples and data required for biomedical studies. **The Danubian Biobank Initiative: Towards Information-based Medicine** established a biobank network focussing on molecular medicine of aging disorders which connects disease-specific collections of different cohorts and controls from universities, associated teaching hospitals, primary prevention programs, and endpoint-related rehabilitation clinics along the Danube river and in neighbouring regions. The scientific network is addressing the field of non-cancer aging-disorders focusing on metabolic overload-related endpoints, including vascular disease, diabetes, metabolic disease, and neurodegenerative disorders. Task forces have been constituted for the relevant topics of the biobank project including patient recruitment, sample and data management, public health, E-Health, epidemiology and genetics, enabling technologies, and research strategies. The project selects the most relevant and promising scientific targets utilizing the core competences developed in the individual partner institutions. This SSA (specific support action) networks medical researchers and basic scientists in this region. Beyond a kick-off meeting, a series of dedicated workshops and conferences have been organised. The **Danubian Biobank Consortium** was formed 2005 (www.danubianbiobank.de) as a network of Danube Universities and associated partner universities between Ulm and Budapest and is financed by local, regional, and national projects and also funded by EU grants (e.g. SSA 018822). From WP4, enabling technologies and in collaboration with the EU-FP6-funded Elife project (contract no. 013032) evolved the successful application of the LipidomicNet project (www.lipidomicnet.org) financed by the FP7 program of the EU with 11.6 Mio Euro for 4 years starting in May 2008, in which 21 academic groups and 5 SMEs focus on lipid droplets and associated diseases as translational research from mouse to man. The Regensburg group is coordinating this effort.

1.1. Project Objectives

The ultimate mission of the Danubian Biobank Consortium was to prepare the ground for health care integrated Biobanking of local and regional health care systems along the Danube through E-health portal structures, IT-based strategies and novel technologies in the field of vascular and metabolic aging disorders.



A major objective of the project was the generation of a common central encrypted patient and sample information database to facilitate international research interactions, combined with local and regional biobanking facilities under common Good Practice (GP) and Standard Operating Procedure (SOP) conditions to move existing health care systems towards personalized healthcare. This process includes the implementation of **local E-health portals** to network health care providers, industry, insurance companies, medical research and public healthcare in a Private Public Partnership (PPP) model to cover jointly the expenses. All information including patient recruitment, blood withdrawal and storage place of the samples is saved in phase I as standardized processing procedures (SPP) for implementation a central IT-based databank in phase II, which is being used in encrypted form for scientific project planning and investigations (study support system database, see www.danubiobank.de). In the local E-health portals the goal is that the actionable health information will be also accessible for direct medical care for the authorized practitioner. In addition to local centers three regional DNA, plasma, and tissue banks in Regensburg, Vienna, and Budapest store samples and encrypted patient data for scientific purposes.

Objective 1: Networking, Sample and Data Management

Networking, bulk data management, sample handling, storage maintenance and retrieval are necessary preconditions for successful biobanking. The university-based diagnostic laboratories within this project provide these core competences. Insufficient sample and data handling due to the lack of GLP/GMP standards and TQM during acquisition and storage were drawbacks for many studies in the past.

Therefore, one major objective was to improve sample/data acquisition and storage by strict application of GMP and GLP rules and to improve data/sample access by using electronic medical records and web-based communication. In addition, sample archiving is now supported by electronic databases with strict enforcement of data privacy and security. By means of advanced information technologies, it is possible to extract actionable health information from the tremendous flood of data, thereby turning the vision of personalized medicine into reality.

Objective 2: Standardization of Clinical and Diagnostic Classification

As a prerequisite required for appropriate data analysis, anamnestic and pedigree information as well as clinical and diagnostic phenotyping have to be as complete and meaningful as possible. Clinical phenotyping will include a basic questionnaire including family history, cognitive evaluation, and physical examination. In addition, endpoint-specific information will complement clinical phenotyping. Regarding diagnostic phenotyping, basic profiles for in situ diagnostics and in vitro laboratory diagnostics will be used for all patients and, in addition, endpoint-specific profiles will be elaborated. The standards for optimised sample and data shall be defined during the second year of this DanuBiobank project in collaboration with the other global (P3G), European (BBMRI) and national (TMF) biobanking projects and the development and compliance to the OECD-guidelines. Standardization also encompasses the precise characterization of control subjects. Endpoint-related rehabilitation centres, outpatient clinics, disease programs of patient organizations and self-care groups, market programs with primarily educational aims and family study programs are regarded as attractive partners for the project and were already contacted.

Objective 3: Public Health, Epidemiology, and Genetics

In addition to proper phenotyping, the scientific value of results depends on three crucial requirements: i) on a sufficient sample size to detect small gene effects - this was addressed by joining the forces of experts in a particular field; ii) the selection of comparison groups or control individuals; iii) on the application of appropriate statistical methods. It is important to reconfirm results from one population in genetically different populations. The Danubian Biobank made it possible to carry out population stratification, compare important findings among different nationalities and study epigenetic influences. The population-wide dimension will also lead to the possibility to use genetic determinants for a public health strategy in the prevention, diagnosis and treatment of the diseases included in this study. In this context an important issue is to meet the patients' concerns about their right to privacy, and the fear of discrimination based on their personal and genotypic data. Experts in genetics/epidemiology will define relevant project areas

which are crucial from a genetic/epidemiological point of view and will develop policies to assure effective public health application.

Objective 4: Enabling Technologies

Joining sample requirements and analytical technologies at the micro- and nano-scale are a task of DanuBiobank. The participating experts define strict sample preparation rules to meet the needs for reliable and robust analyses. In this context, the current networks, i.e. the BayGene network and the GenAU network, will be involved. In the future, these enabling technologies will continuously develop to basic methods that will be available for each patient.

Objective 5: Research Strategy

Researchers of the Danube universities have successfully developed core competences in diabetes-related endpoints, will bundle the existing activities and create a strategy to fully harmonise the biobank infrastructure towards vascular disease, metabolic disease and neurodegenerative disorders. Experts within these medical fields are brought together in this proposal and workshops have been organized to elaborate what direction of research is most likely to bring future breakthroughs.

1.2. Contractors Involved (for the duration of the project)

Part. No.	Participant name	Participant short name	Address	Country
1	Gerd Schmitz	UniReg	University of Regensburg	Germany
2	Oswald Wagner	MedVien	Medical University of Vienna	Austria
3	Balasz Gyorffy	SemmUni	Semmelweis University	Hungary
4	Jaroslav A. Hubacek	IKEM	Inst Clin Exp Medicine	Czech Republic
5	Ivar Klimes	EndoBratis	Academy of Science, Inst. of Experim. Endocrinology	Slovakia
6	Vita Dolzan	UL	University of Ljubljana	Slovenia
7	Wolfgang König, Bernhard Boehm Christian Ludolph	UniUlm	University of Ulm	Germany
8	Jaakko Tuomilehto, Michael Brainin	DonauUni	Danube University	Austria

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Project website: www.danubianbiobank.de

1.3. Work Performed and End Results

1.3.1. General Description of Results

An overview of general project objectives, the project's current relation to the state-of-the-art and a summary of the objectives for the reporting period, work performed, contractors involved and the main achievements in the period, comments on the most important problems during the period including the corrective actions undertaken is given in this section

IT-Structure and Homepage

One central data bank (Regensburg) and three geographically distributed local biobanks (Regensburg, Vienna, and Budapest) have been established following the OECD recommendations (*Draft Guidelines for Human Biobanks and Genetic Research Databases, 2008*) and the collaborative discussions with the BBMRI-consortium. After an assessment of the current information systems, the Danubian Universities with the aid of IT companies (e.g. Siemens, IBM, Telecom international), European projects (e.g. Karolinska Institutet Biobank, UK Biobank), and the P3G consortium are delineating the common IT architecture of the future network. Web-based communication has been realized as a project-driven website within an E-Health portal for the public. Web-based communication (data, video and voice) has been also implemented in the new FP7 EU-project LipidomicNet for communication of the coordinator with the management team and the Task Forces with each other (Webex-platform).

With the **IT-pilot** the consortium showed the feasibility of the Danubian Biobank project on a smaller scale (see "University Hospital of Regensburg, Danubian Biobank, foundation for Public Utility in Molecular Medicine of Aging Disorders, Readiness Assessment"). The IT-pilot was possible through additional funding organized by the Institute for Clinical Chemistry in Regensburg.

The interactive Danubian Biobank website has been launched in January 2006 including a web-based patient health record **Study Support System (SSS)** and the Danubian Biobank Expertise Platform (www.danubianbiobank.de). The web-based and encryptable patient health record study support system allows online recording of patient and family history. The questionnaire is based on a data set that is used by MONICA and follows the main line of studies archived by the observatory of P3G (Public Population Project in Genomics). In Budapest, the components of the interactive Danubian Biobank website were introduced.

The following improvements and new implementations have been done in the Study Support system during the duration of the project:

- Stable implementation of pedigree information and pedigree graphical display of families and records related to family members
- Implementation of bar-coding features
- Implementation of order generation features
- Dynamic search engine
- Graphical user interface improved
- Extracting data for secondary analyses implemented
- Tools for optimized organization of new studies implemented (step by step data entry for study/visit/sample/analysis etc)
- New questionnaires/forms for organization of different studies accessible (see above).
- Secure connection implemented (https-128bit SSA)
- Expansion of registered users demonstrates acceptability of biobank

Biobank prototype development for integrated health care biobanking.

In collaboration with the SME Askion in Gera (www.askion.de) and the Fraunhofer Institute for Cryobiology (Prof. GR Fuhr, Fraunhofer Institute for Biomedical Engineering, IBMT, www.ibmt.fraunhofer.de) the Danubian Biobank Consortium is developing a liquid nitrogen-based roboted biobanking unit for integrated health care biobanks. The project currently applies for additional funding by the BMBF in Germany. This cooperation has led to a new highly competitive EU-FP7 application on Healthcare Integrated Biobanking (HIBconsortium) with 17 academic and industrial partners focussing on "High throughput healthcare integrated biobanking technologies for tissues, cells and body fluids from preanalytics to automated storage, retrieaval and phenotyping". This application, of which Prof. Schmitz is the coordinator, has passed already the first hurdle and is being now submitted (deadline 22nd April 2009) as a full application with good chances to be considered for funding.

Enabling Technologies

The Danubian Biobank Consortium has developed multiple activities to implement novel technologies and SOPs for applications including co-founding of the European Lipidomics Initiative (SSA ELIfe, www.lipidomics.net; www.lipidomics-expertise.de) and the establishment of the public domain, LipidomicNet method-, data- and knowledgebase (www.lipidomicnet.org). The Project-application to the EU on LipidomicNet from the year 2007 (FP7-HEALTH-2007-A (LipidomicNet, N° 202272) was successfully approved and is funded for 4 years beginning May, 2008. The Danubian Biobank consortium established SOPs for lipidomics analysis based on

mass spectrometry, HPTLC and HPLC methods that allow high-throughput analysis of all important molecular lipid species from minor blood sample volumes (plasma and cells). There are strong scientific cooperations, but also activities in E-health, biobanking and formation of a diagnostic center. The next step is networking the triangle Regensburg – Nürnberg/Erlangen – Ingolstadt to establish the Bavarian E-health Network. Standard Operating Procedures (SOP) for EDTA-blood based cellular human monocyte and platelet analysis of parameters relevant for atherosclerosis have been established. Furthermore, also cytomics SOPs for preparative cell fractionation for genomic, proteomic and lipidomic analysis were developed. The consortium helped to introduce a new immuno-magnetic whole blood cell harvest system that needs no precentrifugation prior to magnetic bead separation (autoMACS™ Pro Separator®; www.miltenyibiotec.com) and can be directly integrated into sample processing robotics.

Workup of the Research Modules

Research module 1 (Transdifferentiation and pathomechanisms of organ dysfunction in the metabolic syndrome complex) has been implemented in one of the main projects of the biobank Dresden. One aim was to establish a collection of well phenotyped individuals in different pathopysiological stages of the development of diabetes mellitus. Within this module we are also collaborating with the EU-FP6 EUROSPAN project which investigates 5 genetically isolated populations (healthy individuals, 1,000 each) throughout Europe that represent a unique resource for genomic research. It quantifies genetic variation in genes known to be involved in health and disease and will harness the genetic uniformity within populations and diversity between populations to identify novel variants influencing complex diseases. Our contribution is laboratory phenotyping and the proteomic and lipidomic analysis (lipid profiling) of all 5,000 samples. Furthermore within this module we are involved in the AIDA- Project (Evaluation of the effects of acarbose (Precose®) on gene regulation in the intestinal endothelium in diabetic patients), which is an acarbose intervention trial in type 2 diabetes patients. From the 120 T2D-patients, 60 were subjected to acarbose treatment for 20 weeks and 60 to placebo samples and patientrecords were collected for the Danubian Biobank. We have performed proteomic and lipidomic analyses in the samples (lipid profiling) before and after the treatment.

A ReForM C grant (sponsored by the University of Regensburg) titled “Metabolic effects on the development of chronic diseases in hormone-sensitive organs” has passed successfully in 2005. Insulin resistance, obesity, and dyslipidemia are common features of gynaecological, obstetric, and urological diseases such as fetal growth retardation, preeclampsia, polycystic

ovary syndrome, gestational diabetes, infertility, mastopathy, and breast cancer, or benign prostate hyperplasia.

The research module 3 (Atherogenic vascular disease and blood compartment interactions) is integrated in the FP6-2005-LIFESCIENEHEALTH-6 and is a collaboration with the EU-FP6 project CARDIOGENICS (037593, Prof. Schunkert/Prof. Hengstenberg) in which over 1,000 CHD patients shall be included and analysed. In the collaboration with Prof. Hengstenberg we have recruited 120 CHD patients and performed cellular analyses (mRNA expression profiling with DNA-chips) using immunomagnetically isolated monocytes. Project-Title: Identification of genetic roots of coronary artery disease by combining stepwise genome wide association studies with transcriptomic and functional genomic investigation of relevant genetic variants.

Research module 4 (Genetic background of chronic renal insufficiency and kidney transplantation) is supported by an „Antrag auf Fördermittel im Rahmen der Regensburger Forschungsförderung in der Medizin (ReForM-C)“ which is a grant from the University of Regensburg. The prospective is a diabetes biomarker study, associated with the REgensburg DIAbetes Cohort (REDIAC-1). Members of this consortium are members of the newly founded and nationally funded SFB-Niere at the University of Regensburg.

Research module 5 (Molecular pathomechanisms of neurodegenerative disorders) is worked up in a Consortium. The short title of the work programme is: Functional and Post Genomics in Alzheimer´s Disease: Genetic Predisposition and Common Risk Pathways - Bridging Alzheimer´s Disease, Adipositas, Diabetes Mellitus & Metabolic Syndrome (ALADIN)

1.3.2 Specific Description of Results and Relation to the State-Of-The-Art

Networking, sample and data management logistic and IT issues of biobanking and generation of an interactive website (Objective 1)

The cluster of institutions responsible for Work Package 1 have defined sample processing and sample handling, furthermore implemented efficient quality control during the term of this Specific Support Action. One central data bank (Regensburg) and three geographically distributed local biobanks (Regensburg, Vienna, and Budapest) have been established. Interactive websites have been established (www.danubianbiobank.de, www.lipidomicnet.org) and follow-up EU-FP7-projects have been successfully initiated (LipidomicNet) or are being in

the second round of successful applicatione (HIBconsortium). The following progress has been made in 2006-2008 within the project:

- The consortium and its biobank are partners of the P3G international biobanking activities, the BBMRI-European biobanking activities and the TMF-German local biobanking activities and contribute to the elaboration of data entry documents and guidelines (OECD) for the establishment of biobank structures and safety of handling the samples and records therein.
- The Danubian Biobank Consortium has developed multiple activities to implement novel technologies and SOPs for applications including the confounding of the European Lipidomics Initiative (SSA ELIfe, www.lipidomics.net; www.lipidomics-expertise.de) and the establishment of the public domain, LipidomicNet method-, data- and knowledgebase (www.lipidomicnet.org). The Project-application to the EU on LipidomicNet from the year 2007 (FP7-HEALTH-2007-A (LipidomicNet, N° 202272) was successfully approved and funded for 4 years beginning May, 2008.
- The consortium is involved in the EU-FP6 project EUROSPAN and performs proteomic and lipidomic analysis (lipid profiling) in 5,000 study individuals.
- Furthermore, the consortium is partner in the German stroke study PRoFESS and in the Recall study (PD Dr. Weimar) and performs lipidomic analyses in serum/plasma to identify and validate in-vitro biomarkers.
- Since 2008 we are also involved in the Bavarian Breast Milk Study and perform lipidomic and mass spectrometric analyses (Prof. Fromme).
- In addition, the Danubian Biobank Project has also led to a new highly competitive EU-FP7 application on Healthcare Integrated Biobanking (HIBconsortium) with 17 academic and industrial partners focussing on “High throughput healthcare integrated biobanking technologies for tissues, cells and body fluids from preanalytics to automated storage, retrieaval and phenotyping” (No. 242147-1, FP7-HEALTH-2009-two-stage). This application, of which Prof. Schmitz is the coordinator, has passed already the first hurdle and is being now submitted (deadline 22nd April 2009) as a full application with good chances to be considered for funding.
- Web-based communication (data, video and voice) has been also implemented in the new FP7 EU-project LipidomicNet for communication of the coordinator with the management team and the Task Forces with each other (Webex-platform).
- Further development and improvement of the **Study Support System (SSS)** for sample and data handling. Stable implementation of pedigree information and pedigree graphical

display of families and records related to family members has been achieved as well as bar-coding and order generation features. A dynamic search engine facilitates a convenient and efficient survey, access and extraction of the data for secondary analyses. The graphical user interface has been improved and tools for optimized organization of new studies were implemented (step by step data entry for study/visit/sample/analysis etc). New questionnaires/forms for organization of different studies accessible (see above) are now available. Secure connection was implemented (https-128bit SSA) to guarantee privacy of the data and patient records.

- Expansion of registered users demonstrates acceptability of biobank.
- Several publications, reviews, dissemination advertisement and conferences and workshops helped to make public the Danubian Biobank initiative (see executive summary and workpackages).

The interactive Danubian Biobank website has been launched in January 2006 including a web-based patient health record **Study Support System (SSS)** and the Danubian Biobank Expertise Platform (www.danubianbiobank.de). The web-based patient health record study support system allows online recording of patient and family history. The questionnaire is based on a data set that is used by MONICA and follows the main line of studies archived by the observatory of P3G (Public Population Project in Genomics). In Budapest, the components of the interactive Danubian Biobank website were introduced. The SSS has been considerably improved in the year 2007.

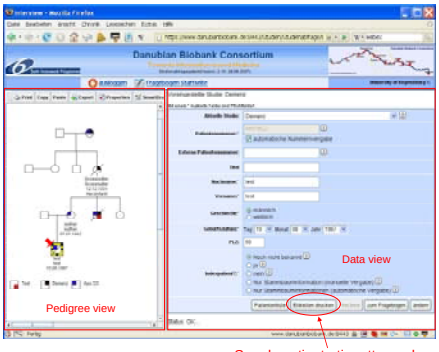
The following improvements and new implementations have been done in the Study Support system during the reporting period 2007 of the project:

- Stable implementation of pedigree information and pedigree graphical display of families and records related to family members
- Implementation of bar-coding features
- Implementation of order generation features
- Dynamic search engine
- Graphical user interface improved
- Extracting data for secondary analyses implemented
- Tools for optimized organization of new studies implemented (step by step data entry for study/visit/sample/analysis etc)
- New questionnaires/forms for organization of different studies accessible (see above).
- Secure connection implemented (https-128bit SSA)

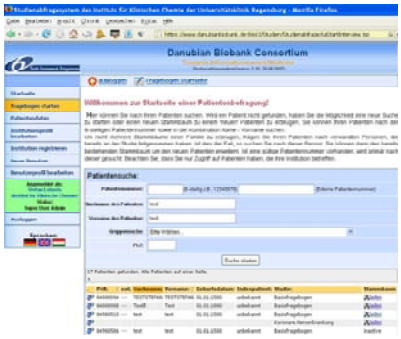
- Expansion of registered users demonstrates acceptability of biobank

The following images represent selected screenshots of the modified and improved Study Support System to give an impression of the features available for efficient sample and patient (records) handling and access to the data.

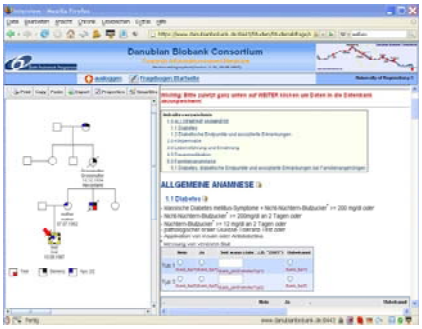
Pedigree drawing and query its corresponding clinical data



Dynamic search engine with quick pop-up informations

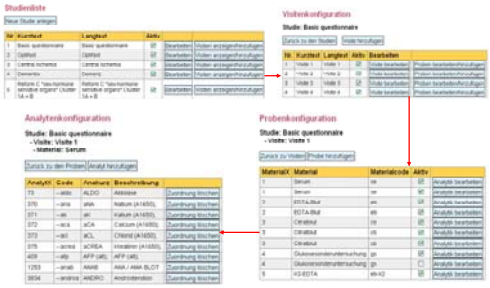


Questionnaire with pedigree view

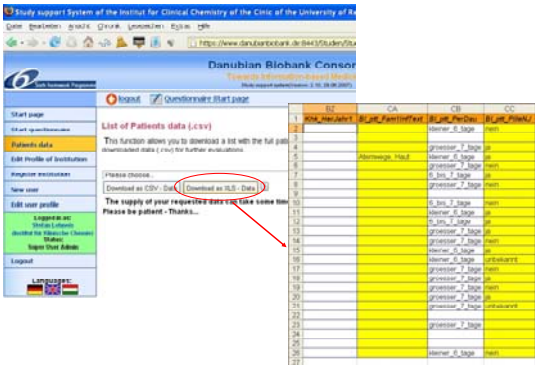


Configuration of new / existing studies

What Study → What Visits → What samples → What analyts



Supply anonymised data for further analysis



Standardization of clinical and diagnostic classification with definition of standards (Objective 2)

Within WP2 the partners have developed the information content for the E-patient record and study support system operating already for all endpoints listed in WP1. In addition disease oriented sample materials and procedures have been defined to consider all preanalytical problems towards SOP establishment. On June 28, 2006 the Danubian Biobank Foundation has been accepted as regular member of the **Public Population Project in Genomics** (P^3G) consortium. In collaboration with the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM) in Hannover (Prof. Borlak / Prof. Fröhlich) and the Fraunhofer Project group in Regensburg (Prof. Borlak / Prof. Schmitz) we are implementing the E-prescribing and Adverse Drug Reaction (ADR) software tool TheraOPT® (http://www.atheso.de/html/uber_uns.html) into the study support system. Similarly the life style record software tool developed at the German Institute of Human Nutrition in Potsdam (Prof. Boeing) has been recently implemented into the Danubian Biobank Consortium study support system. A software tool for the environmental and occupational hazards for the integration into the study support system is under development.

Public health, epidemiology and genetics, including integration of public health survey and population genomics into study design (Objective 3)

In Work package 3 all necessary control cohort issues relevant for the integrated health care case/control strategy of the Danubian Biobank Consortium have been addressed. In the activities within the ESFRI - European Strategy Forum on Research Infrastructures, in the BBMRI - European Bio-banking and molecular resources initiative, Prof. Schmitz is actively involved with a grant application together with Prof. Wichmann (Munich) and Prof. Zatloukal (Graz) and is responsible for parts of deliverable 3.3 in the BBMRI-application. For this deliverable, “Review of technical solutions and quality criteria“.an extensive review on biobanking and preanalytics is being elaborated with the help of partners from the Danubian Biobank Consortium and partners from other Europe-wide activities related to biobanking and preanalytical procedures.

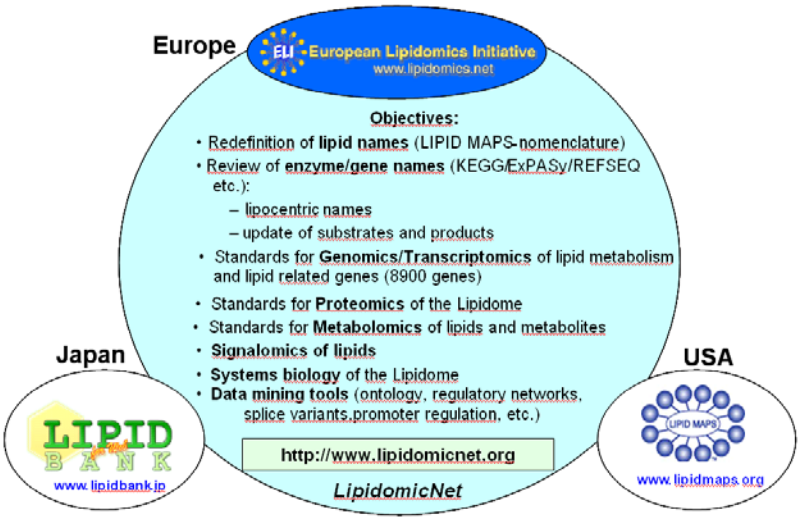
For a collaborative project (Large-scale integrating project) a proposal called “Advice for Scientists/stakeholders on Setting-up and Integrating STandardized Biobanks” (ASSIST-Biobanks) is submitted. The work program topics addressed are integrated in the FP7 topic “HEALTH-2007-2.1.1-1 (Networking biobanking initiatives across Europe), with the aim of developing standards and norms for existing and future human sample biobanks. The coordinating person is Paul Burton (University of Leicester, UK). This application was unfortunately not granted a high priority and was rejected.

Enabling technologies for structural on functional genomics, proteomics, metabolisms, lipid molecular species analysis and systems biology (Objective 4)

Rapidly evolving enabling technologies in the field of genomics, proteomics, metabolomics, and lipidomics are of major importance for sample analysis. Therefore, joining sample requirements and analytical technologies at the micro- and nano-scale are a task of DanuBiobank. The participating experts define strict sample preparation rules to meet the needs for reliable and robust analyses. In this context, the current networks, i.e. the BayGene network and the GenAU network, will be involved. In the future, these enabling technologies will continuously develop to basic methods that will be available for each patient. Objective 4 is implemented through Work Package 4.

The Danubian Biobank Consortium has developed multiple activities to implement novel technologies and SOPs for applications including:

1. Cofounding the European Lipidomics Initiative (SSA ELIfe, www.lipidomics.net; www.lipidomics-expertise.de) and establishment of the public domain, LipidomicNet method, data- and knowledgebase. An application was submitted for the first call in FP7-HEALTH-2007-A (LipidomicNet, N° 202272) in the year 2007 and following first positive evaluation and entering the negotiation phase with the EU in September 2007, was finally approved starting May 2008 with a duration of 4 years and a budget of 11.6 Mio Euro EU-contribition for 26 European groups (21 academia, 5 SMEs) focussing on translational research from mouse to man in the field of lipid droplet formation and human disease (www.lipidomicnet.org). The Danubian Biobank consortium established SOPs for lipidomics analysis based on mass spectrometry, HPTLC and HPLC methods that allows high-throuput analysis of all important lipid molecular species from minor sample volumes.



2. Start up of the Fraunhofer Project Group „Disease and Toxicoproteomics of Aging Disorders" (Prof. Borlak / Prof. Schmitz) (€ 6,2 million) at the campus of the University of Regensburg as a partner of the Danubian Biobank Consortium.
3. Integrated in these local activities at the University Hospital are regional hospitals in Regensburg and specialized medical practices. There are strong scientific cooperations, but also activities in E-health, biobanking and formation of a diagnostic center. The next step is networking the triangle Regensburg – Nürnberg/Erlangen – Ingolstadt to establish the Bavarian E-health Network.
4. Based on a positively decided grant application of the Bavarian Genome Network (BayGene) with a project volume of € 7.4 million the Institute of Functional Genomics headed by Prof. Oefner was founded in 2005. A second BayGene project (€ 3,5 million) on the modeling of complex genomic systems has been recently approved and is directed by the newly appointed W2-professor of biostatistics and information theory of biological systems (Prof. Sprang) within the Institute of Functional Genomics.
5. Standard Operating Procedures (SOP) for EDTA-blood based cellular human monocyte and platelet analysis of parameters relevant for atherosclerosis have been established. Furthermore, also cytomics SOPs for preparative cell fractionation for genomic, proteomic and lipidomic analysis were introduced.
6. We performed feasibility studies for a new immuno-magnetic cell harvest system that needs no precentrifugation prior to magnetic bead separation (autoMACS™ Pro Separator®; www.miltenyibiotec.com) and can be directly integrated into sample processing robotics.
7. In addition the Danubian Biobank Project has also led to a new highly competitive EU-FP7 application on Healthcare Integrated Biobanking (HIBconsortium) with 17 academic and industrial partners focussing on "High throughput healthcare integrated biobanking technologies for tissues, cells and body fluids from preanalytics to automated storage, retrieaval and phenotyping". This application, of which Prof. Schmitz is the coordinator, has passed already the first hurdle and is being now submitted (deadline 22nd April 2009) as a full application with good chances to be considered for funding.

Besides the European Lipidomics Initiative, a Proteomics Initiative was also started in cooperation with the "Deutsche Gesellschaft für Proteomforschung (DGPF)" and the HUPO (human proteome organization). Prof. Schmitz is member of the council of the DGPF and contributor to the "Weissbuch 2007". He organized a workshop on clinical proteomics in

September 2006 in Martinsried (Munich) and during the years 2007/2008 he has worked out a consensus document on clinical and cellular proteomics and a status paper which is going to be submitted for publication as two parts ("Approaching Clinical Proteomics: Current State and Future Fields of Application in Fluid Proteomics" and "Approaching Clinical Proteomics: Current State and Future Fields of Application in Cellular Proteomics") This is in close cooperation with Prof. H. Meyer and Prof. Apweiler (HUPO president) for the international working group on clinical proteomics.

Implementation of the Regensburg E-health portal

The available technologies include high throughput genotyping, DNA-microarrays and Taqman PCR for genetic analysis and MALDI-TOF and the multicolour 2D-Gel Typhoon system for proteomics. The institute has established an elaborated lipidomics platform with high performance gel-filtration chromatography methods, tandem mass spectrometry (ESI-MS/MS, GC-MS), capillary isotachophoresis and gradient gel analysis for lipoprotein subspecies and lipid analysis.

The Danubian Biobank Consortium is in close cooperation with the LipidomicNet Consortium (www.lipidomicNet.org) which has agreed on the development of the following enabling technologies:

Standardisation of high throughput analytical procedures

Standardisation of lipid analysis and analysis of lipid related proteins and genes in a high throughput format for large scale production of reliable and reproducible datasets as the basis for understanding the complexity of diseases of the lipid metabolism. Finding solutions for the difficulties of robotic handling of lipid samples in organic solvents will convert mass spectrometry of lipids into a real high throughput technology. A similar development is expected for the extremely time-consuming processing of image series obtained by automated high content microscopic imaging. Better tools for image processing that are being developed will enable faster screening procedures. Based on unified data formats that will be developed these screens can be cross-correlated and subjected to meta-analysis and will reveal connections that were missed so far. This project part has been expanded in Workpackage 2 of the EU-FP7 LipidomicNet project and represents one of the main goals therein (www.lipidomicnet.org).

Advanced microscopic imaging

In this area, four technologies are supported: Single molecule tracking, label free multi-photon microscopy, freeze fracture electron microscopy and EM tomography. Application of these techniques on neutral lipid accumulations will expand our knowledge by

- pictures of neutral lipid dynamics with unprecedented resolution by single molecule tracking
- detailed insight into lipid droplet formation and turnover in living tissue by label free multiphoton microscopy
- detailed insight into the internal structure of LDs and lamellar bodies by freeze fracture EM
- three dimensional high resolution images of the spatial organisation of lipid droplets in the context of the surrounding organelles cell organelles

This project part has been expanded in Workpackage 2 of the EU-FP7 LipidomicNet project and represents also one of the main goals therein (www.lipidomicnet.org).

This information will set the stage for a cell biological mechanistic interpretation of the data obtained by pathway mapping and other large scale data collections obtained in the other work packages.

Standardised materials

siRNA resources

A centralized resource facility for distribution of siRNA sequences is being established. The facility will save costs to the partner laboratories, accelerate research, and set common standards for efficient and reliable use of this valuable technique by

- Supplying evaluated siRNA sequences in amounts for small scale experiments to partner labs, together with information from evaluation.
- Supplying optimized transfection protocols for several model cell lines

The resource will contain about 1,000 individual accessible sequences (not arrayed like a library) targeting genes in lipid metabolism. The evaluation of sequences will be based on knock-down and efficiency determination by western blotting with antibodies obtained from the partners.

Taqman microfluidic cards

Pathways mapped will be validated by recently presented pre-spotted TaqMan real-time PCR Low-Density Arrays. This method needs only minute amounts of mRNA and at the same time provides a high assay precision. An array for all known human ABC transporters was already validated in human primary monocytes and commercialized (ABI-TLDA on demand). These arrays will be tailored to specific pathways of the lipidome (~4,800 genes described in detail in

LipidomicNet; www.lipidomics-expertise.de) and will speed up research by providing fast and precise data to an affordable price.

Antibody resources:
More than 80 different mouse and human antibodies are already available at the start of the project within the consortium with relevance for cellular lipid homeostasis. Moreover, with the SME partner **Protagen** significant expansion of antibodies and protein expression capacities became available to the consortium

As stated for the Danubian Biobank goals above, standardised materials are also the focus in Workpackage 2 of the EU-FP7 LipidomicNet project (www.lipidomicnet.org).

Survey of expertise is documented by the following activities:

1. April 2007, Opening of LipidomicNet website
2. 2007, E-Health portal pilot installed for local studies (REDEPS, study support system)
3. Since 2006, Implementation of HTS-massspectrometry, flow-cytometry and imaging in our institute
4. Implementation of microscopic imaging
5. Development of TaqMan microfluidic cards in cooperation with ABI (additional grant from ABI for a technician working on microfluidic cards and SNPs

The research strategy of the Danubian Biobank Consortium (Objective 5)
Researchers of the Danube universities have successfully developed core competences in diabetes-related endpoints and have bundled the existing activities and have created a strategy to harmonise the biobank infrastructure. The following medical fields have been addressed: first, vascular disease (e.g. stroke, myocardial infarction, peripheral artery disease, arterial thrombosis, kidney failure), second, metabolic disease (e.g. obesity, diabetes, metabolic syndrome), and third, neurodegenerative disorders (e.g. dementia, Parkinsonism).
Experts within these medical fields have been brought together and workshops have been organized to elaborate what direction of research is most likely to bring future breakthroughs. In particular, the staged approach has been used. This means that specific designs are applied in situations where a primary condition may have a significant genetic component (e.g. hypertension, dyslipidaemia, diabetes, etc.) and this condition leads in some of the affected individuals to a secondary condition (e.g. coronary heart disease, stroke, kidney disease,

dementia, etc.) which also has an independent significant genetic component. In such situations it is important to be able to separate the genetic susceptibility to the primary and secondary conditions adequately. With well phenotyped and sufficiently large biobank material this is possible.

The following five research modules of WP5 reflect the patient recruitment strategy from screening programs and preventive medicine areas.

Research module 1: Transdifferentiation and pathomechanisms of organ dysfunction in the metabolic syndrome complex. Partner 5 (Prof. Klimes, Bratislava) is now partner in LipidomicNet.

Research module 2: Metabolic effects on the development of chronic diseases in sex-hormone-sensitive organs. Prof. Ronningen from the Norwegian Mother and Child Study is now a partner of the HIBconsortium and of LipidomicNet. Dr. Pfeiler, Regensburg (Prof. Ortmann) moved to the AKH-Vienna (partner 2) to build up a biobank related to hormone sensitive organ diseases in Vienna.

Research module 3: Atherogenic vascular disease and blood compartment interactions. Prof. Hengstenberg and Prof. Schmitz, both Regensburg (partner 1) are partners in the Cardiogenics consortium contributing with samples and analyses of CAD-patients.

Research module 4: Genetic background of chronic renal insufficiency and kidney transplantation.

Research module 5: Molecular pathomechanisms of neurodegenerative disorders. Integration of international neurodegenerative biobank and networking activity into the Danubian Biobank Consortium. Prof. Ludolph, Ulm (partner 7) joined this activity by clustering along the Danube experts in neurodegenerative diseases.

A close collaboration and integration with biobank activity in Poland and Russia has been started with Prof. Ludolph, Ulm, Prof. Tomik, Department of Neurology, Jagiellonian University, Krakow; Prof. Baranczyk-Kuzma, Department of Neurology, Medical University of Warsaw; Prof. Skvortsova, Dr. Levitsky, Neurology & Neurosurgery Clinic, Department of Fundamental Neurology, Stroke Institute, Russian State Medical University, Moscow.

Description of the clinical studies of the Danubian Biobank Consortium

A list of all cohorts within the biobank of Regensburg and Vienna can be seen under the Danubian Biobank Homepage (www.danubianbiobank.de)

2. Dissemination and use

Over 2006 to 2008, the results from the specific support action “The Danubian Biobank Initiative: Towards Information Based Medicine” have been disseminated in the open workshops organized by the DanuBiobank, satellite meetings to conferences and in position papers in leading journals. An interactive website is available for registered users with most of it open to the public as well (www.danubianbiobank.de). Relevant information concerning the workshops and the meetings is included in a timely manner in this website. This interactive website is part of an E-Health portal that also considers educational issues (e.g. lifelong learning programs). It addresses general practitioners, nurses, and the informed patient.

The results of DanuBiobank have taken the form of policy statements, reviews of a particular area of research and expertise survey results. The consortium and its biobank are partners of the P3G international biobanking activities, the BBMRI-European biobanking activities and the TMF-German local biobanking activities and contributed to the elaboration of data entry documents and guidelines (OECD) for the establishment of biobank structures and safety of handling the samples and records therein. Our position papers help to draw attention to the research community towards biobanking. Involving actors beyond the founding members is of pivotal importance since population-wide biobanking depends on the involvement of as many initiatives as possible. Although we were proactive in approaching actors beyond the core of the Danubian Biobank, we expect that a sound publicity strategy as proposed herein will serve as an invitation to interested parties like communities, local media, chambers of commerce, public health organizations and patient self care groups (e.g. weight watchers, coronary sport groups).

Exploitation following the project has already taken the form of spin-off consortia aiming to undertake certain joint research activities under national or international funding. The largest consortium ever to be funded by the EU on lipidomics is the recently established LipidomicNet initiative (www.lipidomicnet.org) which focuses on research related to lipid droplets and is coordinated by the coordinator of the Danubian Biobank Prof. Gerd Schmitz, Regensburg (see above). LipidomicNet as a consortium of 26 European groups with an EU-FP7 funding of €11.6 millions for 4 years has started in May 2008. In addition, the consortium is associated with the EU-FP6 projects EUROSPAN (research module 1 of WP5) and CARDIOGENICS (research module 3 of WP5). In addition the Danubian Biobank Project has also led to a new highly competitive EU-FP7 application on Healthcare Integrated Biobanking (HIBconsortium) with 17 academic and industrial partners focussing on “High throughput healthcare integrated biobanking technologies for tissues, cells and body fluids from preanalytics to automated

storage, retrieaval and phenotyping". This application, of which Prof. Schmitz is the coordinator, has passed already the first hurdle and is being now submitted (deadline 22nd April 2009) as a full application with good chances to be considered for funding.

In summary, the action has helped realizing a Biobank model, thereby generating a win-win situation for all stakeholders. The diversity of activities, scientific meetings, networking and policy meetings, a survey of expertise and the publication of position papers not only results in a strategy of research on aging disorders for the direct actors involved, but it also brings attention to the field of biobanking and thus inspires stakeholders to seek contacts and establish strategic alliances.

Workshops and Conferences:

17.01.2007

The members of Work Package 3 Public Health, Epidemiology, and Genetics met on January 17, 2007 in Munich (Germany) at MUNICON Conference Center at Munich Airport. (Prof. Tuomiletho P6, Prof. Meitinger, GSF Munich)

26/27.04.2007

Biobanking and Biorepositories Conference (Amsterdam, oral presentation of Prof. Schmitz on Danubian Biobank and health care)

04/05.05.2007

The Scientific Meeting III of Research Module 5: "Molecular pathomechanisms of neurodegenerative disorders" took place May 4 and 5 in Linz/Austria (Prof. Ludolph, Ulm,

17.-22.06.08

A meeting »Pharmacogenetics in clinical practice« was organised in Ljubljana, Slovenia, on 22. 06. 2007., by Dolzan V.(chair) as a satellite meeting to the 15th International Conference on Cytochromes P450: Biochemistry, Biophysics, Functional Genomics (Bled, 17. 06. – 21. 06. 2007 (Rozman D, chair, Dolzan V, co-chair).

29/30.06.2007

On June 29/30, 2007 a Symposium on Biomarker Research and Biobanking activities was organized by Prof. Schmitz and Prof. Endres (LMU-Munich) together with the Novartis-Foundation for therapeutic research in Nürnberg. From this meeting a bookchapter has been prepared entilteld: Cardiovascular and metabolic system: Biomarker in Diagnostic and Therapy

27.07.2007

Status Meeting Danubian Biobank and oral presentation on the WP5RM2 at the AKH in Vienna (PD Dr. Pfeiler, Vienna and Prof. Schmitz) and planning of the Vienna workshop RM4 (postponed from 27.10.07 to 16.04.2008) and the Bratislava Workshop RM1 (Prof. Klimes P 5) to be held 24.04.08

27.08.2007

On August 27, 2007, the workshop Stroke data banks and genetic biobanking – how to link them for translational research has been organised by Prof. Tuomilehto, Prof. Brainin (Krems) and Prof. Mannhalter (Vienna) in Krems.

21.09.2007

In the course of the common annual conference of the Deutsche Vereinte Gesellschaft für Klinische Chemie und Laborartoriumsmedizin (DGKL) and the Östereichische Gesellschaft für Laboratoriumsmedizin und Klinische Chemie (ÖGLMKC) on September 19-22, 2007 in Vienna, a common session of the Danubian Biobank Cosortium with the “Biobanking and Biomarker Development” has taken place on September 21, 2007. This session was organized by Prof.. Endler and Prof. Wagner from Vienna. The following topics were on the agenda:

1) From Biobanking to Biomarker Development

2) The European Lipidomics Initiative and LipidomicNet provide a lipidomic database for the transcriptomic, proteomic, and lipidmolecular species analysis for clinical lipidomics

3) Pre-analytical strategies for clinical cytomics

13/14.11.2007

Biobanking and Biorepositories meeting in Munich on “refining guidelines and implementing best practice to enhance international co-operation and biobank potential” (Holiday Inn, Munich, one oral presentation of Prof. Schmitz).

18-20.01.2008

Two oral presentation of Prof. Schmitz at the 55th Congress of the ESCC (Cairo). 1. From biobanking to biomarkers, 2. Cytomics as a new field of biomarker development.

03-05.02.2008

Kick-off meeting of the eurIPFnet EU FP7 project (attendance and presentation of Prof. Schmitz on sampling biobanking and analysis for institutional pulmonar fibrosis IPF patients).

14.03.2008

Cooperation meeting on biobanking and lipidomic of Prof. Schmitz with Prof. Yusuke Nakamura (director of the Janpan Biobank and Prof. Masahiro Nishijima (director of Lipidbank, Japan) in Tokio.

31.03-01.04.2008

Meeting of a working group ("Biobanking") in Sulzbach, Germany) Prof. Schmitz)

10.04.2008

Oral presentation of Dr. Munkacsy (P3) on "Tissue conservation technologies for obtaining the highest RNA yields" at a PhD conference. Since then biweekly Telephone conferences were organized with EUROSPAN-Consortium members to prepare common publications.

14/15.04.2008

European biobanking and biorepositories spring meeting, Zurich. Oral presentation of Prof. Schmitz on "From biobanking to Biomarkers".

16.04.2008

Oral presentation of Dr. Munkacsy (P3) on "Danubian biobank research focuses in Budapest" at the Danubian Biobank meeting in Vienna

24.04.2008

On April 24, 2008 a "Danubian Biobank Meeting II" has been organized by Prof. KIimes in Bratislava.

29.04.2008

EU-FP6 EUROSPAN-meeting in Munich. Cooperation talks and progress report on the EUROSPAN contribution of Danubian Biobank partners (Prof. Schmitz).

01/02.05.2008

Oral presentations of Prof. Schmitz on lipidomics and metabolic syndrome associated diseases and patient recruitment at the 43rd DDG Jahrestagung in Munich.

29-31.05.2008

BBMRI-WP3-meeting and P3G-consortium. Meeting of Prof. Schmitz with scientists from the BBMRI and P3G global biobanking initiatives.

12-14.06.2008

8th International Gene Forum 2008 in Tartu, Estonia. Oral presentation of Prof. Schmitz "From Biobanking to Biomarkers".

15-17.06.2008

Kick-off meeting LipidomicNet in Regensburg (Prof. Schmitz)

15-17.09.2008

Bioinformatics-Workshop LipidomicNet in Regensburg (Prof. Schmitz)

10-11.11.2008

First Steering Committee Meeting LipidomicNet in Regensburg (Prof. Schmitz)

Position papers and publications:

- The Danubian Biobank initiative: synchronising the biobanking activities of the Danube universities. Gyorffy B, Rosivall L, Prohaszka Z, Falus A, Füst G, Munkacsy G , Tulassay T. Orv. Hetil. 2007;148:1999-2002 (article in Hungarian)

- Internet-based biobank-registers in Hungary. Vasarhelyi B, Bencsik P, Szmolenszky A, Molnar MJ, Gyorffy B, Kosztolanyi G, Tulassay T, Falus A. Orv. Hetil. 2007;148:939-943 (article in Hungarian)

- The Danubian Biobank Initiative: Towards information-based medicine. Schmitz G. The Parliament Magazine (Politics, Policy and People), 2007;254:65 (Advertisement/Dissemination)

- The Danubian Biobank project. Schmitz G, Aslanidis C, Liebisch G, Orsó E. Stud Health Technol Inform. 2008;134:143-59

- Preparatory paper for the Danube Biobank Project within Section M3 in WP5 on Scientific Strategy (in progress). Brainin M, Matz K, Mannhalter C, Tuomilehto J. (Journal to be defined)

- Healthcare integrated biobanking and biomarker development. Schmitz G. PSCA International (Public Service Review: European Union 15) 2008 (Advertisement/Dissemination)

- Adipose tissue and skeletal muscle plasticity modulates metabolic health, Ukropec J, Ukropcova B, Kurdiova T, Gasperikova D and Klimes I, Archives of Physiology and Biochemistry 2008 /in press/

- From biobanking to biomarkers: The advancement of individualised molecular medicine. Schmitz G. PSCA International (Public Service Review: European Union 15) 2008 (Advertisement/Dissemination)

- Healthcare integrated biobanking: Improving healthcare for future generations. Schmitz G. PSCA International (Public Service Review: European Union 16) 2008 (Advertisement/Dissemination)

- Cardiovascular and metabolic system: Biomarkers in diagnostics and therapy. König W., Hengstenberg C. and Schmitz G. (2008 in preparation).

- Approaching clinical proteomics: Current state and future fields of application in cellular proteomics. Apweiler et al. Cytometry Part A, 2009 (accepted after minor revisions)

- Approaching clinical proteomics: Current state and future fields of application in liquid proteomics. Apweiler et al. (2009 submitted)

- High throughput biobanking: Healthcare integrated biobanking of tissues, cells and body fluids. Schmitz G. PSCA International (Public Service Review: European Union 17, 292-293) 2009 (Advertisement/Dissemination)

- High throughput biobanking: Healthcare integrated biobanking of tissues, cells and body fluids. Schmitz G. PSCA International (Science and Technology Review, ST2) 2009 (Advertisement/Dissemination)