Medical University of Graz

SPIDIA WORKSHOP

Standardisation of Sample Pre-Analytics for Molecular Diagnostics and Biomarker Development

Wednesday, October 10th, 2012
15:00 - 19:00

Medical University of Graz
Institute of Pathology, Lecture Hall
Auenbruggerplatz 25
8036 Graz
Austria

SPIDIA

SEVENTH FRAMEWORK PROGRAMME

SPIDIA WORKSHOP

Standardisation of Sample Pre-Analytics for Molecular Diagnostics and Biomarker Development

In this public workshop scientific key activities and main results of the large-scale European FP7 project SPIDIA (**S**tandardisation and improvement of generic **P**re-analytical tools and procedures for **I**n-vitro **DIA**gnostics, www.spidia.eu), a collaboration of 16 leading academic institutions, international organisations and life sciences companies, are presented, accompanied by talks and discussions with international experts in the field of bio-specimen research, molecular diagnostics and biomarker development. SPIDIA aims at providing the scientific evidence for new European standards and norms for sample pre-analytics.

Scientific Topics include

- Critical pre-analytical variables of biological samples
- Novel tissue fixation technologies
- RNA analysis in blood and tissue samples
- Protein and phospho-protein profiles
- Metabolomics
- Development and validation of molecular biomarkers

Organisation& Contact
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PROGRAMME

15:00-15:05	**Opening words** Irmgard Lippe, Vice rector of the Medical University of Graz, Austria
15:05-15:25	**EU SPIDIA Project Update – Standardisation and Improvement of Generic Pre-analytical Tools and Procedures for In-Vitro Diagnostics** Uwe Oelmüller, SPIDIA Coordinator, QIAGEN GmbH, Hilden, Germany
15:25-15:45	**Biospecimen Research at the U.S. National Cancer Institute** Helen Moore, Director of the NCI Biospecimen Research Network (BRN), Bethesda, USA
15:45-16:05	**The Role of Interdisciplinary Networks in Molecular Diagnostics Biomarker Validation** François Rousseau, Québec University Hospital Centre, Québec, Canada
16:05-16:25	**The Pre-Analytical Phase for Molecular Methods in Blood Samples** Mario Pazzagli, University of Florence, Italy
16:25-16:35	**RNA Quality Biomarkers to Monitor Pre-Analytical Variation in Blood Samples** Hui Zhang, DiaGenic ASA, Oslo, Norway
16:35-16:55	**Pre-Analytical Parameters Impacting on Molecular Analyses of Tissues** Kurt Zatloukal, Medical University of Graz, Austria
16:55-17:15	****** Coffee break ******
17:15-17:25	**Impact of Pre-Analytical Factors on Protein and Phospho-Protein Profiles in Tissue Samples** Karl-Friedrich Becker, Technical University of Munich, Germany
17:25-17:35	**Improvements of Tissue Pre-Analytics for High Quality Tissue-Based Molecular Studies** Christian Viertler, Medical University of Graz, Austria
17:35-17:45	**Adapting Routine Tissue Freezing Protocols for a Better Collection for Medical Research Purposes** Peter Riegman, Erasmus Medical Center, Rotterdam, The Netherlands
17:45-18:05	**Molecular Analysis for Clinical Research and Diagnostics in Archive Tissues** Giorgio Stanta, Coordinator IMPACTS Project, University of Triest, Italy
18:05-18:25	**Biobank Graz: Automation and Effective Sampling and Storage to Maximize Sample Quality** Berthold Huppertz, Director of the Biobank Graz, Medical University of Graz, Austria
18:25-18:35	**Don't Alter the Individual Metabolome** Paola Turano, CERM, University of Florence, Italy
18:35-18:55	**Quality Control Needs of Biobank Samples for Reproducible Metabolomics** Beate Kamlage, Metanomics GmbH, Berlin, Germany
18:55-19:00	**Closing words** Uwe Oelmüller, SPIDIA coordinator, QIAGEN GmbH, Hilden, Germany

EU SPIDIA Project Update – Standardisation and Improvement of Generic Pre- Analytical Tools and Procedures for In-Vitro Diagnostics

Uwe Oelmüller, SPIDIA Coordinator, QIAGEN GmbH, Hilden, Germany

Molecular in vitro diagnostics and biomedical research have allowed great progress in medicine. Further progress is expected by new technologies analyzing cellular biomolecule profiles such as nucleic acids, proteins, and metabolites. New biomarkers based on these biomolecule classes including disease specific biosignatures will be key value drivers for future personalized medicine and improved health care. Studies have demonstrated that profiles of these molecules as well as their qualities can change significantly during sample collection, processing, transport, storage, archiving and biomolecule isolation thus making diagnostics or research unreliable or even impossible. High quality clinical samples with preserved bioanalyte profiles are therefore critical to diagnostics, research, and biobanking. Access to such high quality samples is one of the major hurdles for the identification and validation of novel biomarkers. International initiatives for biospecimen research, for developing new pre-analytical technologies and tools, and for standardizing pre-analytical workflows by new international evidence based guidelines have therefore been recently started. The four-year large-scale integrating research project SPIDIA within the European Union FP7 program is one of the major contributors to these efforts. The project is supported by 7 private research and diagnostic companies, 8 public research organizations, including universities, hospitals, and biobanks, and 1 European standards organization, the European Committee for Standardization CEN. An introduction into the SPIDIA program status will be presented.

Biospecimen Research at the U.S. National Cancer Institute

Helen Moore, Director of the NCI Biospecimen Research Network (BRN), Bethesda, USA

The Role of Interdisciplinary Networks in Molecular Diagnostics Biomarker Validation

François Rousseau, Québec University Hospital Centre, Québec, Canada

Appropriate evidence-based validation of biomarkers prior to their introduction into medical practice is recognized by international bodies such as the OECD as being of critical importance to insure sustainability of health care systems across the world through an efficient use of resources. Molecular diagnostics biomarker validation pose different types of challenges, some of which are specific to the type of technologies employed. Since these markers are used in several fields of laboratory medicine, and given the very broad types of expertise needed to generate the evidence-base needed for biomarker validation, interdisciplinary networks of investigators, decision-makers and end-users are seen as one of the mechanisms to integrate and streamline the validation process. The CanGèneTest/APOGÉE-Net Research and Knowledge Network on Genetic Health Services is such an organization. The concept behind this Network and examples of its realizations will be presented.

The Pre-Analytical Phase for Molecular Methods in Blood Samples

M. Pazzagli[1], F. Malentacchi[1], L. Simi[1], C. Orlando[1], R. Wyrich[2], K. Günther[2], P. Verderio[3], S. Pizzamiglio[3], C. M. Ciniselli[3], A. Tichopad[4], M. Kubista[4], L. Barraud[5] and S. Gelmini[1]

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Background: Molecular Diagnostics have allowed a great progress in medicine but their use can be limited by the lack of guidelines for collection, handling, stabilisation and storage of biosamples. The development of evidence-based quality guidelines for blood samples requires the identification of critical steps in the pre-analytical procedure that need further development.

Methods: To reach this goal, within the EU granted project SPIDIA (www.spidia.eu) it was planned the implementation of a panel of Pan- European

external quality assurance schemes (EQAs) specifically designated for blood DNA, cell-free DNA and blood RNA. With the EFCC support, more than 300 applications have been collected from 30 different European countries. The participants to the SPIDIA EQAs received the same sample/s (whole blood, plasma) and performed the extraction procedure. Participants then sent back the extracted DNA/RNA to SPIDIA for further analysis, plus details about reagents and protocols used for the extraction phase.
Results: At SPIDIA facilities, the extracted samples have been investigated for quality/quantity/integrity and stability and then the participants have received a report and a qualitative "score" which includes the comparison of the performance of the single laboratory with that of the other participants. Further analysis of the SPIDIA-EQAs results has allowed to identify some of the variables that can mainly affect the analytical validity of the molecular tests. This evaluation will be the basis for the preparation of a draft for the guidelines for the pre-analytical phase.
Conclusions: This project is the basis for the preparation of evidence-based guidelines for the pre-analytical phase and for the preparation of documents scientifically mature enough to serve as a basis for assessment of a CEN/TC official document and potentially serve as a basis for standardisation activities.

RNA Quality Biomarkers to Monitor Pre-Analytical Variation in Blood Samples

Zhang Hui[1], Rian Edith[1], Kruhøffer Mogens[2], Korenková Vlasta[3], Björkman Jens[4], Švec David[4], Sjoback Robert[4], Verderio Paolo[5], Pizzamiglio Sara[5], Wyrich Ralf[6], Oelmueller Uwe[6]
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Quality control of blood sample handling is an important step to achieve reliable data in clinical diagnostics. Several reports have shown that degradation and deregulation processes occur during pre-analytical procedures. However, no reliable biomarkers have been discovered to date that can be used to identify changes occurring during pre-analytical sample handling of blood. An important objective for SPIDIA is to identify RNA quality biomarkers to monitor pre-analytical variation in blood samples. We have identified and

validated a set of biomarker candidates for monitoring pre-analytical variation of RNA in blood samples collected in EDTA and PAXgene tubes. The candidates were identified by microarray analysis. In this talk, we will present the 1) optimization of the qPCR assays design of the identified biomarker candidates, 2) evaluation of the precision of the biomarker assays and 3) pre-validation and extended validation of the biomarkers' abilities to demonstrate an ongoing degradation /deregulation in blood sample RNA.

Pre-Analytical Parameters Impacting on Molecular Analyses of Tissues

Kurt Zatloukal, Medical University of Graz, Austria

Impact of Pre-Analytical Factors on Protein and Phospho-protein Profiles in Tissue Samples

Karl-Friedrich Becker, Technical University of Munich, Germany

Precise quantitation of protein biomarkers in tissues has great potential for the development of personalized molecular targeted therapies. However, little is known about the impact of pre-analytical factors on protein stability. One aim of our activity is to develop standard operating procedures for asservation of tissue specimen. In this study we focussed on potential changes of phospho-proteins with regard to delayed fixation. Murine and rat liver samples were collected under different ischemic conditions and either cryopreserved, formalin-fixed or fixed with the PAXgene Tissue System, a new formalin-free fixative, that is being evaluated by the European FP7 consortium SPIDIA (www.spidia.eu). The phosphoproteome of biological triplicates was analyzed using quantitative mass spectrometry (LC-MS/MS) and reverse phase protein array (RPPA) technology. The phosphoproteomic analysis of ischemic mouse liver tissue samples indicated no significant global alterations of more than 5000 phosphosite-ratios analysed during 60 minutes of delayed cryopreservation. The analysis of differently fixed ischemic rat liver tissue specimens by RPPA revealed similar results, as phosphoproteins showed little changes during the time-course experiment, independent of the preservation method applied. We could not detect significant global changes of the phospho-protein profiles, neither with a targeted nor with a non-targeted approach, although undirected fluctuations were seen that did not reach statistical significance. We conclude that delayed preservation

results in a complex expression pattern of the phosphoproteome in tissue samples.

Improvements of Tissue Pre-Analytics for High Quality Tissue-Bases Molecular Studies

Viertler C[1], Groelz D[2], Kashofer K[1], Gündisch S[3], Riegman P[4], Winther R[5], Wyrich R[6], Kruhoffer M[7], Becker KF[3], Oelmüller U[6], Zatloukal K[1]

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Background: Molecular characterization of human disease relies on the analysis of multiple parameters, from morphological features to a broad spectrum of biomolecules. Histopathological diagnosis is routinely based on formaldehyde-fixed and paraffin-embedded (FFPE) tissues but it is known that formalin fixation impairs molecular analyses which typically require frozen tissue samples. Within the European FP7 project SPIDIA we developed and tested a new technology for combined histological and molecular analyses from paraffin-embedded tissue samples (PAXgene Tissue) and evaluated the impact of several pre-analytical variables on the quality of tissue-based molecular studies.

Methods: Matched samples from different human (non-)malignant tissues were fixed in buffered formaldehyde, non-crosslinking fixatives including the PAXgene Tissue System, and snap-frozen tissue samples served as reference. In a comparative study the quality of morphology, antigenicity and different biomolecules was investigated, in particular of nucleic acids.

Results: Established methods for RNA quality control (e.g. 28s:18s ratio, RIN value) were well-suited for frozen tissue, but to estimate the suitability of impaired RNA from paraffin-embedded tissues for downstream applications, we recommend a more detailed analysis, like a qPCR assay based on different amplicon length. qPCR results were sensitive to pre-analytical procedures such as time or type of fixation and storage conditions. In contrast to FFPE, PAXgene-fixed and paraffin-embedded (PFPE) samples revealed excellent preservation of (mi)RNA, high molecular weight DNA and phosphoproteins

that was similar to cryopreserved samples, representing the gold standard for molecular analyses. Furthermore, critical pre-analytical variables such as prolonged fixation time did not compromise the quality of RNA-based molecular studies from PFPE samples.
Conclusion: Pre-analytical procedures have a major impact on the quality of tissue-based molecular studies. The excellent preservation of biomolecules, in combination with good morphology, in PFPE samples provides new opportunities for comprehensive tissue diagnostics, biomarker discovery and reliable molecular analyses whenever a collection of snap-frozen material is impossible.

Adapting Routine Tissue Freezing Protocols for a Better Collection for Medical Research Purposes

Peter Riegman, Erasmus Medical Center, Rotterdam, The Netherlands

Routine pathology tissue samples are mostly formalin fixed and paraffin embedded for diagnostic purposes. An increasing number of protocols also need tissue samples to be frozen for diagnostic purposes. The aim of freezing can be to enable fast histology for fast diagnostics for instance during operation for which the outcome depends on the results of pathology findings. Freezing can also be needed for additional diagnostic tests. Alterations of the freezing process can lead to a very usable collection of tissues for medical research. Alternatives for frozen tissues were studied within the SPIDIA project. Conservation of DNA, RNA and proteins is better in frozen tissues compared to FFPE materials and is seen as the golden standard, whereas for morphology, FFPE is the golden standard. Both can be used for medical research as secondary use of residual material following often an easier regulatory regime. Precondition is that the material is obtained from surgical specimens that were send to the pathology lab for diagnostic purposes. Freezing samples of adjacent unaffected, premalignant and of more patients can follow the same regulatory regime as long as it concerns residual tissues. The important factor here is that it concerns only material obtained through routine curative and diagnostic pathways and no extra material is taken from the patient.
For tissues in particular histology can be crucial for the relation to molecular findings and is therefore very important to conserve properly using snap freezing techniques, whereas in the routine setting the material might only need to be frozen for further chemical testing.

Equal high quality is important for the stability of the outcome of the tests therefore variations in the pre-analytical phase should be avoided wherever possible by using Standard Operating Procedures that allow future cooperation with other institutes and therefore follow the international guidelines, best practices and common minimal standards for biobanking.
One part in the pre-analytical phase of a frozen tissue sample can however not be covered by SOP's: the patient and the treatment. Variation of, surgical procedure, time needed to perform the surgical procedure, administered drugs prior to the intervention, patient condition and genetic background (patient groups). However recording the different parameters in this phase and biobanks having access to the records can be crucial to identify possible outliers or causes of institutional bias.
For future sharing of samples between different institutes it is important to adjust also other variations that can be found in the transport conditions of the fresh tissue to the pathologist, time before freezing (cold ischemia) and treatment of the surgical specimen after receipt like aliquoting in different sizes. Several experiments have been done within SPIDIA to investigate if there are perhaps optimal conditions that could be recommended to future tissue collections.

Molecular Analysis for Clinical Research and Diagnostics in Archive Tissues

Giorgio Stanta, Coordinator IMPACTS Project, Dept. of Medical Sciences, University of Trieste, Italy

In any hospital the clinical tissues taken from patients for diagnosis or surgical treatment are fixed and paraffin embedded. In many European countries these tissues are stored, sometimes for decades, in the pathology archives, after few sections are cut for diagnosis. A huge quantity of tissues is available for research and these represent the real clinical heterogeneity of human diseases, especially in oncology. These are the only tissues available for patients for any molecular analysis. The development of translational research and reverse translational research in these tissues can give results that can be applied as prognostic and predictive biomarkers to the patient in a very short time, because the methods and tissues are the same as those used at the diagnostic level. The European IMPACTS group is working in this field of preservation and standardization of fixed and paraffin embedded tissues and in

collaboration with the industry vacuum machines and standard fixation apparatus were developed. Another important problem in these archive tissues is to always maintain a significant proportion of patients' tissues for further diagnostic analysis. For this reason the IMPACTS group developed the use of tissue arrayers to obtain microdissected areas of tissues to be analyzed for clinical research. Standardization of the methods of analysis is another important issue to be developed especially for genomics and proteomics.
These studies can be used as reverse translational research because new and unexpected results can be referred back to basic research to be functionally explained.

Biobank Graz: Automation and Effective Sampling and Storage to Maximize Sample Quality

Berthold Huppertz, Director of the Biobank Graz, Medical University of Graz, Austria

The massively increasing number of samples in a variety of biobanks implicates the development of sophisticated storage technologies. This is especially important to increase the number of high quality samples and maintain their quality during storage. The consequence is the change from manual storage systems to semi or fully automated systems to store samples at room temperature, minus 80°C as well as in the gas phase of liquid nitrogen. At all levels the Biobank Graz has cooperated with respective companies and has developed systems for high quality sample storage.

Don't Alter the Individual Metabolome

Paola Turano, CERM, University of Florence, Italy

It is rapidly becoming possible to measure tens of metabolites in small samples of biological fluids or tissues via nuclear magnetic resonance (NMR). This makes it possible to assess the metabolic status of an organ or of an organism. The relations between metabolomics profiles of different individuals allow us the early diagnosis of diseases, their progression, the response to treatment. At the basis of this approach there is the need that the preanalytical treatment does not alter the status of the biospecimen. SPIDIA has contributed to

the definition of appropriate sample collection, handling and storage procedures that preserve the precious individual metabolic signature.

Quality Control Needs of Biobank Samples for Reproducible Metabolomics

Beate Kamlage, Oliver Schmitz, Philipp Schatz
Metanomics Health GmbH, Berlin, Germany

Metanomics Health GmbH, a BASF Group company, is the world leading company offering targeted and non-targeted metabolite profiling to healthcare customers in industry and academia as well as funding and conducting a comprehensive diagnostic biomarker program, addressing open questions of high and unmet medical need. Research in the healthcare area like identification and validation of new diagnostic biomarkers, drug target discovery and treatment monitoring approaches often starts with the analysis of existing biobank samples. The quality of these biobank samples can be impaired by various pre-analytical sample processing steps that will confound the analytical results and decrease the value of research if not identified and addressed properly. Therefore, reproducible and meaningful biomarker research demands standardized protocols for sample handling (quality assurance) as well as quality control of biobank samples.
Metabolite profiling, also known as "metabolomics", is a well-suited technology to support the identification of technical biomarkers for the quality assessment of biobank samples due to its high sensitivity plus the broad coverage of physiological and chemical processes. Assurance and control of sample quality with respect to various pre-analytical processes and compliance to standardized protocols is cost and time-saving. The presentation will focus on quality assessment of human blood plasma samples by metabolite profiling based on examples of biobank-related variability and confounding factors like time and temperature of sample processing.

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About the project

SPIDIA is a 54-month collaborative project which unites public and private researchers to perform interdisciplinary translational research. SPIDIA addresses the objectives of the EU Seventh Framework Programme "HEALTH" priority 1 of the Cooperation programme and more precisely the "Detection, Diagnosis and Monitoring" topic dedicated to multidisciplinary research. More specifically, SPIDIA fully meets the expectations of the line, HEALTH-2007-1.2-5, concerning the "Standardisation and improvement of pre-analytical procedures for in vitro diagnostics".

SPIDIA will contribute to the standardisation and improvement of procedures and tools for pre-analytical intervention. The individual steps, such as sample handling, stabilisation and storage, will be standardised and integrated in one holistic process combining classical and molecular diagnostics. Furthermore, potential new biological biomarkers will be discovered and validated. Finally, SPIDIA aims at developing and validating the necessary guidelines and tools that will make possible the production of new knowledge and its translation into practical applications in the area of health and medicine.

About us

The SPIDIA consortium has been formed by merging the complementary expertise of the different consortium partners. SPIDIA involves 16 partners from 11 different European countries (DE, AT, IT, SE, CH, NO, DK, FR, CZ, BE and NE). It consists of 7 private research companies (including 4 SMEs and 3 pre-analytical diagnostic tool developers), and 8 public research organisations, including universities (molecular biologists, clinical chemists, spectroscopists, pathologists, etc), hospitals, 3 biobanks, and 1 European Standards Organisation, CEN. vFurthermore, the consortium has been extended by a Club of Interest in order to have an optimal dissemination of the obtained results.

The SPIDIA project is coordinated by QIAGEN GmbH, Germany, a life science company with an extensive know how and expertise in sample preparation and stabilisation of biomolecules. Partner NOVAMEN is responsible for the effective project management of SPIDIA and has long standing experience in research management, project and finance controlling as well as meeting organisation for funded projects.

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