



Sixth Framework Programme for Quality of Life and
Management of Living Resources

Project no. LSHG-CT-2006-037686

EMERALD

Empowering the Microarray-Based
European Research Area to Take a Lead in
Development and Exploitation

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Partner responsible: NTNU

Minutes of EMERALD associated activities at ESF Functional Genomics and Disease conference. Innsbruck. Austria October 1-4, 2008

Introduction:

The European Science Foundation (ESF) is an association of 77 member organizations devoted to scientific research in 30 European countries. The 3rd ESF Conference on Functional Genomics and Disease (<http://www.esfg2008.org/>) was held in Innsbruck Austria 1-4 October 2008. The developments in functional genomics technologies together with the expanding concept of systems biology have led to exciting possibilities for the understanding of disease mechanisms. Following two highly successful conferences in Prague and Oslo, this conference brought together world leaders in the field to discuss the challenges ahead and technologies that will lead to novel solutions. The meeting covered several different topics with keynote, plenary lectures and a set of symposia. About 500 people participated at the meeting.

According to our project plan and also taking into account the advice of the proposal reviewers, EMERALD should team up with the European scientific community, schedule meetings and promote the importance of quality issues related to the microarray technology.

EMERALD hosted a symposia session (Microarray Quality and Clinical Applications) where we briefly presented the aim of our project and had invited four internationally recognized researchers to talk about issues that need to be solved, before we will be able to really use microarray technology in the clinic. About 150 people participated at the EMERALD session. The feedback on the session was very good, both from the audience, the speakers and the organizers of the conference. We were actually asked if we want to have a similar session at the next ESF Functional Genomics and Disease conference in 2010.

In addition to the EMERALD session we presented the project and disseminated results by a poster (see attachment 1) where we specifically presented some results from WP1 focusing on quality metrics and the development of additional MGED ontology (people responsible: Wolfgang Huber, Audrey Kauffmann, Helen Parkinson and James Malone all EBI). We also distributed a leaflet describing the EMERALD project, including all contact information for EMERALD (see attachment 2).

Summary of talks at the EMERALD Microarray Quality and Clinical Application session:

The session was chaired by Arne Sandvik and he started the session by a 5 minutes presentation of the EMERALD project objectives and status.

11.00 – 11.30 Fraser Symmans (Texas): Use of multigene signatures in clinical samples of breast cancer.

In his talk Fraser focused on how standardization of all procedures from sampling to data analysis need to be controlled to get reliable results. Microarray-based analysis of preoperative needle biopsies from breast cancer, as used in his laboratory, was discussed. He also presented results from a study (in collaboration with the US MAQC project) where they investigated the effects of tumor heterogeneity and inter-laboratory differences when evaluating clinical breast cancer samples.

An abstract for this talk can be found in attachment 4.

11.30 – 12.00 Catherine Nguyen (Marseille): Why is the adoption of DNA microarrays for clinical diagnostics so slow?

Catherine's talked about the history of microarray use in clinical application. She made a point of that even though this technology now have been out running for more than 10 years only a few assays have found the way to the clinic. This includes gene expression, copy number variation and SNP analysis. For example the first chip for diagnostic uses was FDA approved in 2005 and the first based on gene expression in 2007. She speculated that the slow evolution of such array based diagnostic tools is a result of the high cost of this analysis. The cost is now much lower and the data quality and reproducibility is better, so it is believed that an increased used was predicted. Alternatively high throughput sequencing will take over, but this technology will probably see many of the same challenges as the microarray technology, so it is reasonable that it will take time to develop new diagnostic tool with this technology too.

An abstract for this talk can be found in attachment 4.

12.00 - 12.30 Therese Sørli (Oslo): Using whole-genome microarrays to profile breast tumors: aspects of data quality and clinical usefulness.

Therese talked about how her research group has used microarray technology as a useful tool in studying genomic profiles of human breast cancer samples. She pointed out several steps in the procedures, from study design, RNA isolation, hybridization to data analysis, where quality control and standardization of procedures/protocols were important factors in generating good and reproducible data. One of the factors which introduced much noise in their set up was array batch effect. However, this was not very critical because it can be corrected by data normalization. Therese concluded that the quality of their microarray data was generally good and that they were able to identify groups of ductal carcinomas with an aggressive phenotype.

An abstract for this talk can be found in attachment 4.

12.30 – 13.00 Jean Gabert (Marseille): Standardisation and external quality controls for gene expression measurements in the clinic: lessons from BCR ABL dosage in the tyrosine kinase inhibitors era.


Jean talked about his experiences with standardization and external quality controls of RT-PCR assays for clinical applications. He used the measurement of BCR ABL transcripts as an example and their experience is that this kind of quality control is not easy but absolutely necessary. The standardization and quality control of RT-PCR assays have been used more extensively than for microarray. Standardization and quality control of microarray technology have therefore probably a lot to learn of this effort that is done for RT-PCR. Jean also mentioned the importance of availability of reference materials and “spikes”/internal control that can be sent out to labs world wide. This is actually one of the scopes of the EMERALD project and we hope to be able to contribute on this in the future.

An abstract for this talk can be found in attachment 4.

Final remark:

Altogether, EMERALD was very visible at the conference and we were able to communicate our mission and results of our work to the European scientific community. Our participation was a success in relation to how much attention we had, with a relatively high number of attendees at the session. All parties were very satisfied with the session and the talks. Overall we conclude that this meeting was very useful for our project.

Attachment 1: EMERALD poster presented at ESF Functional Genomics and Disease, 2008.



EMERALD

Enhancing microarray data quality

The EMERALD consortium*

Project objectives

The European Union FP6 Coordination Action (CA) EMERALD, aims to establish and disseminate quality metrics (QM), microarray standards and best laboratory practices throughout the European microarray community. This will allow microarray data production to take full advantage of QA/QC, thereby significantly enhancing the quality of microarray data and setting a precedent for other array-based technologies. Data quality and meta data (documentation) are key to all microarray data generation and analysis, to ensure that maximum information can be extracted from the data. The need to reanalyse and reproduce data spawned a grassroots movement, now the MGED Society that established guidelines for experiment description (MIAME) and a structured data exchange model (IMAGE-ML). MGED initiatives have predominantly been focused on data context, and its scope has only recently been extended to included data content. Quality and integrity of microarray data compendia (e.g. in ArrayExpress) are major determinants for information and extraction model building. High quality data will constitute one of the pillars of the systems biology. This CA is designed to structure and amalgamate ongoing efforts across the Europe community, in close association with MGED and the ERCC.

Coordination and dissemination activities

Coordination activities are defined in six main areas relevant for microarray analysis: Development of quality metrics, ontology for data description, implementation of standards and best practices, selection of standards that are candidates for European Reference Materials, impact of QA/QC on data information content, and dissemination of QA/QC principles to novel experimental high-throughput techniques for the different -omics domains. These activities are made up of six work packages (WP).

WP1: Quality Metrics and Ontologies (EBI). The objective of this WP is to develop and disseminate quality metrics and tools for determining data quality and communicating data transformations. As part of the MGED ontology, a normalisation and transformation ontology (NTO) is being developed to describe data transformations (Figure 1). Recent information about the ontology work can be found at our web page: http://www.microarray-quality.org/ontology_work.html. We are also developing a new Bioconductor package named arrayQualityMetrics, that provides a HTML report with diagnostic plots for one or dual color microarray data (Figure 2-4). The quality report contains the evaluation of different categories of quality metrics. The individual array quality is controlled by M versus A plots. The existence of spatial effects is checked by image representations of the arrays. Scatter plots are used to assess the reproducibility of the experiments. Boxplots and density plots allows the control of the homogeneity between the experiments. The report also contains a study of the GC content effects and the mapping of the reporters to test the array platform quality. A heatmap representing the distance between the samples allows the evaluation of the biological signal to noise ratio. In the case of Affymetrix experiments, some quality controls usually used for this platform are added to the report, such as Relative Log Expression (RLE) or Normalized Unscaled Standard Error (NUSE) plots for instance. This report can be used as a first step of the microarray analysis or to compare the efficiency of different methods of normalization. The quality metrics report will also be useful to assess the quality of public data in the context of meta-analysis for instance. Recent information can be found at our web page: http://www.microarray-quality.org/quality_metrics.html. **People responsible: Wolfgang Huber, Audrey Kauffmann, Helen Parkinson and James Malone (EBI).**

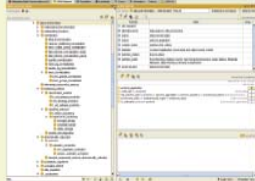


Figure 1. A Normalisation and Transformation Ontology (NTO).

As part of the MGED ontology, a normalisation and transformation ontology is being developed to describe data transformations. The ontology will cover aspects of microarray data such as normalisation techniques, quality metrics and quality control and data transformation. The development of this ontology will employ several strategies that will be the subject of workshop group discussion, and it will include analysis of current vocabularies and text mining of relevant literature.

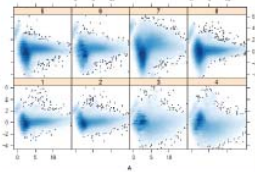


Figure 2. Represents MA plot for each array. MA-plots are useful for pairwise comparisons between arrays. Rather than comparing each array to every other array, here we compare each array to a single median "pseudo"-array. Typically, we expect the mass of the distribution in an MA-plot to be concentrated along the $M = 0$ axis, and there should be no trend in the mean of M as a function of A. Note that a bigger width of the plot of the M-distribution at the lower end of the A scale does not necessarily imply that the variance of the M-distribution is larger at the lower end of the A scale: the visual impression might simply be caused by the fact that there is more data at the lower end of the A scale. To visualize whether there is a trend in the variance of M as a function of A, consider plotting M versus $\ln(A)$.

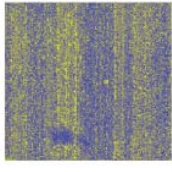


Figure 3. Intensity representation on the array (spatial plots). False color representations of the spatial intensity distributions of each arrays. These graphical representation permit to show problems during the experimentation such as fingerprints, artificial gradient or dye specific failure for instance.

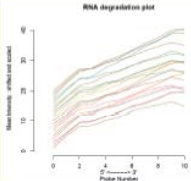


Figure 4. RNA digestion plot. In this plot each array is represented by a single line. It is important to identify any array(s) that has a slope which is very different from the others. The indication is that the RNA used for that array has potentially been handled quite differently from the other arrays.

WP2: Standards (LGC). The objective of this work package is to plan and advocate the use of standards by the microarray community. This will involve the identification of suitable reference materials (spikes, reference RNA), the assessment of analytical "best practice" guidelines and standardised approaches to experimental design and execution.

WP3: Organisation and dissemination (NTNU). The purpose of WP3 is to organise and structure the community "pull". First, we will identify and bring together the key players in the field of transcriptome microarray use and further development. We will disseminate the results of WP1 and WP2 to the community through a series of workshops. Updated information will be available through our web page: www.microarray-quality.org.

WP4: Data Quality and Systems Biology (VIB). WP4 will assess the impact of QM-based filtering and general QA/QC implementation on the performance of various mining and modelling approaches of such data compendia.

WP5: Standards and European legislation (IRMM). The purpose of WP5 is to take the QA/QC criteria analysed, developed and discussed in the previous 4 work packages and translate these into commutability criteria for microarray-relevant reference materials. These criteria will form the basis for independent projects, aimed at developing and distributing European reference materials.

WP6: New Technologies (UU). A survey of new applications and development efforts in microarray technologies will be performed, in order to identify key academic and commercial players (research groups, users, product and service providers).

*Project partners

Martin Kuiper - VIB, Belgium and NTNU, Norway.
Arne K. Sandvik - NTNU, Norway.
Alvis Brazma - EBI, United Kingdom.
Carole Foy - LGC, United Kingdom.

Joaquin Dopazo - CIPF, Spain.
Lazlo Puskas - HAS, Hungary.
Heinz Schimmel - IRMM, Belgium.
Ulf Landegren - UU, Sweden.

If you are interested to participate, or have information relevant to this project, please contact:

Project coordinator:
Martin Kuiper (kuiper@nt.ntnu.no)



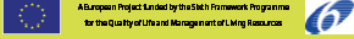
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EMERALD is funded by the Sixth Framework Programme for the Quality of Life and Management of Living Resources. Project no. LSHG-CT-2005-037689. Scientific officer: Christina Kyriakopoulou (@ec.europa.eu)

www.microarray-quality.org

Attachment 2: EMERALD leaflet distributed at ESF Functional Genomics and Disease, 2008.

<p>Project management</p> <p>The project is managed by a project board which has representatives of the eight partners:</p> <p>Martin Kulper Flanders Institute for Biotechnology, VIB, Gent, Belgium and Norwegian University of Science and Technology, NTNU, Norway.</p> <p>Arae K. Sandvik Norwegian University of Science and Technology, NTNU, Norway.</p> <p>Alvis Brazma European Bioinformatics Institute, EBI, United Kingdom.</p> <p>Carole Fey LGC, United Kingdom.</p> <p>Joaquín Dopazo Centro de Investigación Príncipe Felipe, Spain.</p> <p>László Puskas Biological Research Center of the Hungarian Academy of Sciences, Hungary.</p> <p>Helmut Schirrmel Institute for Reference Materials and Measurements, Belgium.</p> <p>Ulf Landegren Uppsala University, Sweden.</p> <p>The project management is assisted by a scientific advisory board:</p> <p>Frank Holsteg Utrecht University, Netherlands.</p> <p>Helen Causton Imperial College London, United Kingdom.</p> <p>Rafael Irizarry Johns Hopkins University, United States.</p> <p>Joerg Hohensee German Cancer Research Center, DKFZ, Germany.</p> <p>Astrid Lagreid Norwegian University of Science and Technology, Norway.</p> <p>Marc Salit National Institute of Standards and Technology, NIST, United States.</p> 	 <p>EMERALD</p> <p>A European Project funded by the Sixth Framework Programme for the Quality of Life and Management of Living Resources Project no. LSHG-CT-2006-037689 Scientific officer: Christina Kyriakopoulou (@ec.europe.eu)</p>  <p>Contact:</p> <p>Project coordinator: Martin Kulper Norwegian University of Science and Technology (NTNU), Department of Biology, Realfagbygget, NTNU, 7491 Trondheim, Norway. Email: kulper@nt.ntnu.no Phone +47 73550348 Fax +47 73596100</p> <p>Project fellows: Vidar Belsvåg Dept. of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Medisinsk Teknisk Forskningscenter Olav Kyrres gt.9, 7489 Trondheim, Norway Email: vidarbelsvag@ntnu.no Phone +47 73598615 Fax +47 72576400 and Ewa Sugajska VB Department of Plant Systems Biology, UGent-VIB Research Building FSVM, Technologiepark 927, BE-9052 GENT, Belgium Email: ewslug@psb.ugent.be Phone +32 93313823 Fax +32 93313809</p>	 <p>A European Project funded by the Sixth Framework Programme for the Quality of Life and Management of Living Resources</p>  <p>EMERALD</p> <p>European Project on Standards and Standardisation of Microarray Technology and Data Analysis</p>
<p>www.microarray-quality.org</p>	<p>www.microarray-quality.org</p>	<p>www.microarray-quality.org</p>

Project objectives

This European Union Framework Program 6 Coordination Action (CA) will serve to establish and disseminate quality metrics (QM), microarray standards and best laboratory practices throughout the European microarray community. This will allow microarray data production governed by QA/QC, significantly enhancing the quality of microarray data and setting a precedent for other array-based technologies. Over the last 15 years microarray technology has proved the method of choice for capturing molecular biological data in a massively parallel fashion. Data quality and meta-data (documentation) are key to all microarray data generation and analysis, to ensure that maximum information can be extracted from the data. Very early in the development of microarray-based transcript profiling the microarray community has realised the importance of structured documentation accompanying microarray

www.microarray-quality.org

data. The need to reanalyse and reproduce data spawned a 'grassroots movement', now the MGED Society that established guidelines for experiment description (MIAME) and a structured data exchange model (MAGE-ML). MGED initiatives have predominantly been focused on data context, and has only recently been extended to include data content. Quality and integrity of microarray data compendia (e.g. in ArrayExpress) are major determinants for information extraction model building and high quality data will be one of the pillars of systems biology. This CA is designed to structure and amalgamate ongoing efforts across Europe, in close association with MGED and the ERCC.

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Work packages

WP1: Quality Metrics and Ontologies (EQO). The objective of this WP is to develop and disseminate quality metrics and tools for determining data quality and communicating data transformations. An Ontology for describing microarray experiments and Normalization and Transformation is now under development (http://www.microarray-quality.org/ontology_work.html). And recently a new Bioconductor package, named `arrayQualityMetrics` (<http://bioconductor.org/packages/2.1/bioc/html/arrayQualityMetrics.html>) is released, that provides a HTML report with diagnostic plots for one or dual color microarray data. The quality report contains the evaluation of the individual array quality, the existence of spatial effects, the reproducibility of the experiments, the homogeneity between the experiments, the GC content effects, the mapping of the reporters, the evaluation of the biological signal to noise ratio. This report can be used as a first step of the microarray analysis or to compare the efficiency of different methods of normalisation.

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WP4: Data Quality and Systems Biology (VIB). WP4 will assess the impact of QM-based filtering and general QA/QC implementation on the performance of various mining and modelling approaches of such data compendia.

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WP6: New Technologies (IUG). A survey of new applications and development efforts in microarray technologies will be performed, in order to identify key academic and commercial players (research groups, users, product and service providers).

EMERALD workshops

WS4: Launch of EMERALD arrayQualityMetrics system (in collaboration with MGED11, 1-5 September 2008, Riva Del Garda Trentino, Italy).

WS5: Microarrays and clinical applications (in collaboration with the 3rd ISF Conference on Functional Genomics and Disease, 1-4 October 2008, Innsbruck, Austria).

WS6: Data quality and Systems biology (in collaboration with the 4th EMBO Conference: From Functional Genomics to Systems Biology, 15-18 November 2008, Heidelberg, Germany).

WS7: Data quality Control and Transformation workshop (in collaboration with the 8th international conference for the Critical Assessment of Microarray Data Analysis CAMDA, 4-6 December, Vienna, Austria, 2008).

WS8: Ontology workshop (November 2008, EBI, Hinxton UK).

WS9: Towards federal standards (planned Spring 2009).

WS10: Implications for new technologies (planned Spring 2009).

WS11: Dissemination of results to larger community (planned Autumn 2009).

Web pages relevant for the project

EMERALD (www.microarray-quality.org)
Microarray Gene Expression Data (MGED) Society (www.mged.org)
National Institute of Standards and Technology (NIST) (www.nist.gov)
External RNA Control Consortium (ERCC) (www.csl.nist.gov/biotech/Cell&TissueMeasurements/GeneExpression/ERCC.html)
Microarray Quality Control (MAQC) project (www.fda.gov/oc/science/centers/toxicoinformatics/maqc/)

Attachment 3. Invited speaker's biographies.

Jean Gabert

AP-HM , Université de la Méditerranée
Faculté de Médecine Nord Bd Pierre
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gaberttournesol@aol.com



Jean Gabert has spent 10 years in the Cancer Center in Marseille as assistant professor in haematology. He is now and since 1999 Professor of biochemistry and molecular Biology, head of the department. He did his PhD in Immunology. His work has always been in the transfer research and availability for patients of new molecular tests allowing improving health care. He has been the coordinator of a very successful European network under the Europe Against Cancer program (SANCO Commission). Recipient of the INPI PACA price for

his university patents for RNA dosage and quantification by real time PCR (RQ PCR). In this context, he is a member of the international expert group for BCR ABL dosage by RQ PCR.

Catherine Nguyen

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Catherine Nguyen is the transcriptome leader in Marseille of the Marseille-Nice Genopole. This team possesses the skills and the experience to conduct all the microarrays experiments. Indeed, Catherine Nguyen is a head of a unit dedicated to functional genomics studies (TAGC laboratory). Up to know, this laboratory count more than 25 persons involved in genetic, genomic, bioinformatics. TAGC laboratory is associated to a transcriptome facility running by Béatrice Loriod which is in charge of the facility at the Luminy campus. This platform is nationally recognized as a platform for functional genomics studies within different research organizations in France.

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Therese Sørlie, PhD, Department of Genetics, Norwegian Radium Hospital. Researcher position with grants from the Norwegian Cancer Society and the Norwegian Research Council. Also affiliated to the Department of Informatics at the University of Oslo as adjunct associate professor. Part of CAST, a government-funded research and innovation center on cancer stem cells. Postdoctoral position at Stanford University with Professor David Botstein. Research interests in breast cancer genomics.

Fraser Symmans

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Dr. W. Fraser Symmans is Professor of Pathology at The University of Texas M.D. Anderson Cancer Center where he practices Breast Surgical Pathology and Cytopathology. Dr. Symmans received his medical degree from the University of Auckland, New Zealand in 1987. He completed his residency training in Anatomical Pathology at Columbia University College of Physicians and Surgeons, New York City and fellowship training in Cytopathology at M.D. Anderson Cancer Center, Houston. Dr. Symmans joined the faculty of New York University Medical Center in 1993 and moved to M.D. Anderson Cancer Center in 2000.

Dr. Symmans' research is focused on breast cancer, with specific emphasis on neoadjuvant (pre-operative) treatment trials for evaluation of chemosensitivity and development of diagnostic tests to select the most effective treatments for individuals with breast cancer. Dr Symmans has adapted genomic technologies to clinical needle biopsies of breast cancer in order to use gene expression profiling to identify important genes for response to chemotherapy. This research program has recruited many women in clinical trials and has identified new molecular targets of diagnostic, prevention, and possible therapeutic relevance. He has published more than 80 peer reviewed articles as well as reviews and book chapters. He has received research funding from the National Cancer Institute, Breast Cancer Research Foundation, Susan G. Komen Foundation and the Department of Defense.

Attachment 4: Abstracts of the talks

S3/1

Use of multigene signatures in clinical samples of breast cancer

Fraser Symmans¹, C. Hatzis², Lajos Pusztai¹

¹ UT M.D. Anderson Cancer Center, Houston, Texas

² Nuvera Biosciences, Inc.

A potential advantage of diagnostic tests based on genomic

microarrays is that different results, including measurement of receptor targets, prognostic tests, as well as endocrine- and chemotherapy-sensitivity predictions can be applied to the data from a single assay from a single specimen. Furthermore, diagnostic specimens of breast cancer are commonly needle biopsies. We obtain clinical needle biopsies of breast cancer specifically for microarray-based gene expression profiling in the context of clinical trials. Microarray-based gene expression levels for receptor therapeutic targets (ESR1 and ERBB2, respectively) from these samples accurately represent tumor receptor status determined from standard pathological assays. Multigene indices to predict tumoral sensitivity to endocrine treatment (SET index), and pathologic response to pre-operative paclitaxel/FAC chemotherapy, have demonstrated accuracy and are entering prospective clinical trials. However, genomic testing of prospective clinical samples introduces a different balance of contributions from variables affecting quality control, compared to studies using archival tumor tissue samples. Issues with tumor sampling are likely to outweigh those of macromolecule preservation. We have compared matched cytologic and tissue samples from breast cancers, and have initiated studies to further investigate the effects of tumor heterogeneity and inter-laboratory differences when evaluating clinical breast cancer samples.

S3/2

Why is the adoption of DNA microarrays for clinical diagnostics so slow?

B. Jordan

Marseille-Nice Genopole

Clinical applications of DNA arrays have been discussed for the last ten years as if they were "almost there" – particularly so for expression profiling of tumours, that appeared particularly promising for prognostic and predictive information. However the actual use of these systems in a clinical context is still limited. The first FDA approval of a DNA array as an in vitro diagnostic device occurred at the beginning of 2005, and the first approval of a system based on expression profiling early in 2007; however, adoption of these tests is slow and high-volume sales have not yet been achieved. In fact, several established array manufacturers have recently abandoned the field. This has to do with several issues:

The difference between mutation detection or deletion/duplication ascertainment ("genotyping arrays"), where clinical correlates are already known, and expression profiling where clinical significance must be established;

Widely different needs in diagnostics versus research: robustness, ease of operation and cost, and a requirement for information that actually supports a clinical decision to treat or not to treat, or to treat differentially;

Data quality and reproducibility, now much improved (viz. results of the MAQC consortium), but still requiring highly trained personnel and rigorous operating procedures;

Recent development of high-speed, affordable genome sequencing providing competition to research and clinical DNA array applications. Nevertheless, several types of application are catching on, in particular the global assessment of genome alterations by arrayCGH. Multiplex disease testing, pathogen identification and some expression profiling applications are also beginning to be adopted, but the road to wide acceptance may be long and will require careful attention to the points mentioned above.

Symposia speakers

S3/3

Using whole-genome microarrays to profile breast tumors: aspects of data quality and clinical usefulness

T. Sørlie

Norwegian Radium Hospital, Oslo

Genomic profiling using microarrays has proven extremely valuable in studying human tumors and for extracting biological information that is useful for understanding tumor development and for improving patient management. The nature of the technology in generating massive amounts of data in a parallel fashion, establishes a need for quality controls (QC) and standards in the experimental design and data processing and analysis. Current microarray suppliers offer whole genome microarrays with a number of features for QC. We have analyzed breast tumors from two patient cohorts using microarrays from Agilent and AB, and performed thorough analyses to investigate whether tumor cell percentages, amplification or hybridization dates, cRNA amplification yield, RNA quality, or microarray lot-numbers showed any systematic effects on the microarray data. Some batch effects were found, however, replicate sample hybridization showed good correlation between different array batches. Tumor samples used in microarray experiments are usually grossly dissected, yielding RNA from various types of cells. We used the information on tumor and stroma cell content in the statistical testing models to find significant genes associated with distant metastasis. Moreover, by analyzing and comparing gene expression profiles from ductal carcinoma in situ (DCIS) and small invasive tumors, we have identified a group of DCIS with an aggressive phenotype. Such biological information could be exploited to identify those patients with in situ lesions who need additional follow-up.

S3/4

Standardisation and external quality controls for gene expression measurements in the clinic: lessons from BCR ABL dosage in the tyrosine kinase inhibitors era.

N. Beauvais^{1,2}, P. Matejtschuk³, J. Gabert^{1,2}

¹ UMAGT, IFR Jean Roche, Université de la Méditerranée, Marseille France

² Biochemistry and Molecular Biology laboratory, Hôpital Nord, APHM, Marseille France

³ National Institute of Biological Standards and Controls (NIBSC), South Mimms UK

Standardisation and external quality controls are part of the routine in clinical biochemistry since years. International standards and external quality control rounds are absolutely warranted for any new biological marker for its worldwide use in the clinic. Taking the measurement of BCR ABL transcripts (M-BCR) as a model, we developed freeze dried cells that can be sent worldwide at room temperature. During the meeting will be reported our efforts in this field at the regional, national and international levels.