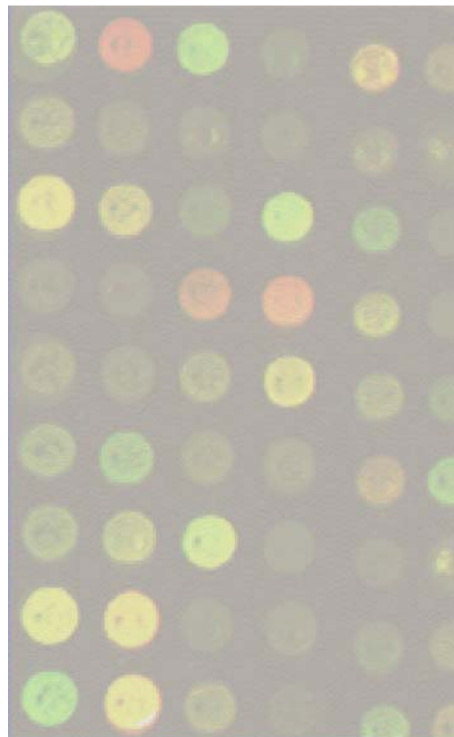
Epidemiology and Gene Arrays in Mammary Gland Research

COST Action B20
Mammary development, function and cancer

European Cooperation in the Field of Scientific and Technical Research



10th and 11th of May 2002 Utrecht University

Androclus Building, Faculty of Veterinary Medicine

Yalelaan 8, 3584 CM Utrecht, The Netherlands

3rd Management Committee Meeting

only for members of the Management Committee

Agenda

Friday 10th May

09.00 Welcome to participants

1. Adoption of the Agenda
2. Adoption of the Minutes of the 2nd MCM, Ayr
3. Introduction of the new Scientific Officer; information from the COST Secretariat
4. Status of COST B20 Action
5. Information from the Working Groups
6. STSM
7. E-mail list, web site
8. Laboratory directory
9. Place and date of next meetings
10. Any other business

12.00 Get-together lunch

Scientific programme

(Titles of presentations may be prone to changes)

Friday 10th May

In the morning, there will be a management committee meeting from 9.00 until 12.00 only for members of the MC.

12.00 Get-together lunch

Session 1 – Epidemiology

Chair: Liliane Rosetta (France)

13.00 – 13.45 Matti Rookus (Amsterdam, NLD), Epidemiology of breast cancer.
13.45 – 14.30 Peter Boyle (Milan, ITA), Lactation and breast cancer risk.

14.30 – 15.00 Coffee break

Session 2 - Array technology (1)

Chair: Armand Sanchez (Spain)
15.00 – 15.45 Finian Martin (Dublin, IRL), Gene expression in the post-natal mouse mammary gland.
15.30 – 16.15 Mari Smits (Lelystad, NLD) Development of microarrays for pigs and chicken.
16.15 – 17.30 Alexandre Caetano (Brasilia, Brazil) Development of porcine ovary arrays.

Afterwards refreshments will be served. At 19.00 a dinner is scheduled at the Hotel "Biltsche Hoek". Please register for this event using your registration form.

Saturday 11th May

Session 3 – Array technology (2)

Chair: Cees Cornelisse (The Netherlands)

09.00 – 09.40 Patrice Martin (Jouy-en-Josas, FRA), Mammary cDNA arrays in domestic animals.
09.40 – 10.20 Tom van Wezel (Leiden, NLD), Expression-based positional cloning of breast tumour suppressor genes on chromosome arm 16q.

10.20 – 10.30 Coffee break

Session 4 – Array technology (continued)
10.30 – 11.10 David Vetrie (Cambridge, GBR), Development of a microarray core facility.
11.10 – 11.50 Christine Steinhoff (Berlin, DEU), Data analysis of cDNA microarrays.
11.50 – 12.30 Jose Palacios (Madrid, ESP), The use of the CNIO Oncochip.

12.30 – 13.00 Lunch

Session 5 – Array technology in mammary cancer

Chair: Joyce Taylor Papadimitriou (United Kingdom)

13.00 – 13.40 Peter Devilee (Leiden, NLD), Association between BRCA1 and BRCA2 mutations and cancer phenotype.
13.40 – 14.10 Henri Magdelenat (Paris, FRA), Spiceome and splice variant arrays in breast cancer.
14.10 – 14.40 Olivier Delattre (Paris, FRA), Comparative Genomic Hybridisation arrays.
14.40 – 15.30 Marc van de Vijver (Amsterdam, NLD), Prediction of clinical outcome by gene expression profiling.

15.30 – 16.00 Coffee/Tea break

After 16.00 there is the possibility to discus further in small groups management committee matters and for the people involved in the proposal for functional genomics of gender-specific cancers a renewed application for the 6th EU programme.

Conference Abstracts

Epidemiology and Gene Arrays in Mammary Gland Research

Gene Expression in the Post-natal Mouse Mammary Gland

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We present a 'work in progress' report on an analysis of gene expression at five time points during the cycle of post-natal mammary gland development using Affymetrix oligonucleotide microarrays representative of 12,800 expressed genes. We examined gene expression in three-week-old virgin mammary gland, 5/6-week peri-pubertal mammary gland (gland rich in terminal end buds and active in mammary tree expansion through the fat pad), 12-14 day pregnant gland, 3-18h resuckled ('re-differentiated'), 40h-involuting gland and 2-day involuting mouse mammary gland. The data was scaled, normalized and subjected to clustering analysis using the GeneSpring suite of programs. In additions, lists of genes whose expression was increased or decreased 2-fold at one time-point relative to the other four were also created. Cohorts of genes whose expression were previously associated with particular stages of the mammary gland cycle of development were correctly identified and the expression of groups of genes of related function clustered to individual stages of development.

In particular, we have further analysed three transcripts whose expression linked to the 5/6-week peri-pubertal mammary gland. *cited 1* is an estrogen receptor-associated transcriptional activator; we found its expression tightly associated with the 5/6-week virgin gland. mSFRP4, the soluble frizzled receptor whose expression has previously been associated with epithelial apoptosis was found on RT-PCR verification to be expressed in the early virgin gland (3- and 5-wk). Finally, we found connexin 43 to be expressed in the 5/6 wk and pregnant gland and to be consistently identified in an expressed gene subtraction study as associated with mammary epithelial cells cultured in the absence of an extracellular matrix. Subsequent immunocytochemical analysis shows connexin 43 to be selectively expressed in myoepithelial cells in the involuting gland (but not in lactation) and in myoepithelial cells and cap cells of the terminal end buds of the 5/6 wk-virgin gland.

Expression-based positional cloning of breast tumour suppressor genes on chromosome arm 16q

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The long arm of chromosome 16 contains at least two separate smallest regions of overlap (SRO) at 16q22.1 and 16q24.3, involved in LOH in breast cancer [1,2]. In spite of extensive mutation analysis many genes, including all known transcripts at 16q24.3, the TSG(s) at chromosome 16q remain elusive. In lobular breast cancer we unmasked E-cadherin at 16q22.1 as a major target for LOH showing inactivating mutations in about 60% of the tumours [3]. The majority of cancers however are of the ductal subtype and these tumours do not harbour E-cadherin mutations so other target genes are most likely affected in these tumours. Due to the biological complexity of LOH data, the precise boundaries of the SROs remain uncertain. Furthermore the majority of the tumours have LOH of a large region at 16q. Thus the reliability of SROs as sole starting point for positional cloning can be questioned. Here we propose a novel "brute force" expression based positional cloning approach to identify the breast cancer TSG(s) at 16q.

By means of cDNA microarray analysis of all the genes located at 16q, the gene-set that is expressed in breast epithelium and that shows repeatedly decreased expression in breast tumours is selected. A cDNA microarray containing al the genes at chromosome 16q is constructed. For selection of genes, all data available from electronic databases, large-scale sequencing efforts and gene-predictions were used. Arrays are hybridised with RNA from normal breast epithelium and normal breast cell lines versus respectively breast tumours and tumour cell lines with and without LOH at 16q.

The candidate genes will be screened by high throughput mutation screening using fluorescent CSGE (conformation sensitive gel electrophoresis) in a breast cancer cell line panel with 16q homozygosity and in a panel of 50 tumours. These tumours represent different histological subtypes and show LOH at the gene locus, preferably restricted to the region that harbours the candidate gene.

Association between BRCA1 and BRCA2 mutations and cancer phenotype

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Approximately 15% of all breast cancer patients have a positive family history for the disease. BRCA1 and BRCA2 are two genes that explain major proportions of families with multiple cases of early-onset breast and/or ovarian cancer. Female carriers of mutations in BRCA1 en BRCA2 have up to 80% risk developing breast cancer before age 70. In most cases, breast cancer develops premenopausally. Female carriers are also at 40-63% to develop ovarian cancer before age 70. Disease outcome in carriers is partly determined by the position of the mutation in the gene. In addition, there is some evidence that genetic variation in other genes might influence this.

Breast cancer in BRCA1-carriers is characterized by more mitoses (per 10 hpf), and a stronger lymphocytic infiltrate as compared to non-BRCA1/non-BRCA2 breast cancers. Almost all tumours are negative for ER and PgR. Breast tumours developing in BRCA2-carriers display less tubule formation than sporadic breast cancer. Both BRCA1- and BRCA2-related breast tumours are more often high grade, and have higher proportions showing continuous pushing margins. Two recent gene expression-profiling studies also underscore that BRCA1- and BRCA2-related breast tumours are distinct entities relative to sporadic cancers.

All these factors suggest that BRCA1/2-related breast cancer have a relatively poor prognosis, but existing literature on this topic is contradictory. Some studies show better survival, other worse survival of BRCA1/2-related breast cancer. BRCA1 en BRCA2 are involved in DNA damage repair which may have implications for radiotherapy.

Spliceome and splice variant arrays in breast cancer

Henri Magdelenat[1] , Patricia de Cremoux[1], Sandra Pommey[2], Brigitta Brinkman[2], Jean Marc Extra[1], Jonathan Kearsey[2], Pascale Fehlbaum[1], Xavier Sastre-Garau[1], Laurent Bracco[2]
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mRNA splicing plays a major role in expanding protein diversity of higher eukaryotes, affecting about 50 % of human genes at a variable degree of complexity. Changes in mRNA splicing occur during development, and is differentially regulated in various organs. Splicing alterations results in structurally and functionally altered proteins and are associated with a number of diseases. RNA splicing alterations occur frequently during carcinogenesis (ex WT1) and tumour progression (ex CD44) and are associated with resistance to chemotherapy.
ExonHit Therapeutics has developed an experimental approach that allows genome-wide identification of alternative RNA processing events, which characterize a given biological situation. This technique, called DATAS ("Differential Analysis of Transcripts with Alternative Splicing”), has been used to isolate tumour specific splice variants.
A specific-specific cDNA library of 682 splice events has been constructed using the DATAS technology. The principle of DATAS is to hybridise cDNA from one biological condition with mRNA from the second and vice-versa. These hybrids are then treated with RNase H to release mRNA that does not hybridise within the heteroduplex. These released mRNAs, that encode qualitative differences between the two conditions, are isolated, reverse transcribed, cloned and collected into libraries. All single clones constituting the library are spotted as PCR products on nylon membranes (arrays). The genetic profile of individual tumours can be obtained by hybridisation of the arrays with ^{33}P-labeled cDNA derived from the specific. Array results were analysed using the Genemath software (Applied Maths)
A prospective clinical evaluation is currently performed with a specifically designed prospective clinical trial including 100 patients with non-operable breast cancer who received FEC100 neo-adjuvant chemotherapy regimen. RNA was extracted from the residual specific tissue taken from patients after completion of chemotherapy. An interim analysis on 24 specific samples (14 non responders, 10 responders) has been performed. This analysis resulted in the identification of 48 gene fragments (36 known and 12 unknown genes) that were able to segregate partial responders from non-responders.
Conclusion: We present here the first demonstration that “spliceomic” profiles derived from DATAS technology can discriminate partial responders from non-responders to a given modality of primary medical treatment of breast cancer. It will be further evaluated in a new prospective trial, for its utility in predicting responder status before treatment.

Poster Session

Epidemiology and Gene Arrays in Mammary Gland Research

DNA array and real-time PCR – an optimal combination!
The use of real-time (kinetic) quantitative PCR to validate cDNA array results

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The application of the real-time (kinetic) PCR to amplify cDNA products reverse transcribed from mRNA (RT) and microarray technology is on the way to become routine tools in molecular biology. They are both well suited to study gene expression, but each methodology has its specific advantages and disadvantages. Microarray technology is ideal to screen a lot of genes in one step (>10,000 gene transcripts) and kinetic RT-PCR is very sensitive, highly quantitative and requires up to 1000-fold less RNA. Both allow a relative and accurate quantification of mRNA molecules with a sufficiently high repeatability and low variability.
But accurate quantification of nucleic acids requires a reproducible methodology and an adequate mathematical model for data analysis. The particular topics of the relative quantification in microarray and kinetic PCR technology of a target gene transcript in comparison to a reference gene transcript or housekeeping gene are described. Therefore a new mathematical model and software is presented. The relative expression ratio **(R)** is calculated from the kinetic PCR efficiencies **(E)** and the crossing point **(CP)** deviation **(ΔCP)** of an unknown sample versus a control. This model needs no calibration curve. Control levels were included in the model to standardize each reaction run with respect to RNA integrity, sample loading and inter-PCR variations. High accuracy and reproducibility (<2.5% variation) were reached in LightCycler® RT-PCR using the established mathematical model (Pfaffl, NAR 2001). **R** of a target gene is expressed in a *sample* versus a *control* in comparison to a reference gene. E_{target} = real-time PCR efficiency of target gene transcript; E_{ref} = real-time PCR efficiency of reference gene transcript; ΔCP_{target} = CP deviation of *control* - *sample* of target gene transcript; ΔCP_{ref} = CP deviation of *control* - *sample* of reference gene transcript.

$$R = \frac{(E_{target})^{\Delta CP_{target}\,(control\,-\,sample)}}{(E_{ref})^{\Delta CP_{ref}\,(control\,-\,sample)}}$$

An Excel® based *Relative Expression Software Tool (REST ©)* is now available, which calculates **E** and **R** of various (<16) samples and four target genes (Pfaffl et al., NAR 2002). Relative expression ratio is tested for significance compared to control on the basis of an *Pair Wise Fixed Reallocation Randomisation Test ©.*

$$R = \frac{(E_{target})^{\Delta CP_{target}\,(MEAN\ control\,-\,MEAN\ sample)}}{(E_{ref})^{\Delta CP_{ref}\,(MEAN\ control\,-\,MEAN\ sample)}}$$

Using this approach, to screen the tissue specific expression levels by microarray and confirm the results by kinetic RT-PCR and REST © is a powerful and optimal combination. The advantages of both quantification systems were added - high throughput of the microarray and sensitivity of the real-time RT-PCR. The latest software version of REST and examples for the correct use can be downloaded at: http://www.wzw.tum.de/gene-quantification/

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