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# International Conference on the Biology of the Mammary Gland. Tours, France (16-18 September 1999)

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# Introduction

The European Co-operation in the field of Scientific and Technical Research (COST) programme is one of the so-called 'horizontal activities' within the European Union (EU) system of support for scientific research, technology and development. It is the purpose of individual COST Actions to establish networks of co-operation and collaboration between interested researchers (in COST-eligible countries that have signed-up to the appropriate Memorandum of Understanding) in the particular area of science addressed by the Action. In general, the European Commission will maintain support for viable COST Actions for up to 5 years. In June 1995, COST Action 825 'Mammary Gland Biology' was inaugurated. This International Conference was organized by COST Action 825 and, as its timing indicates, was planned to be a culminating activity of the network and one against which its success could be measured.

Around 175 participants gathered in France's Loire Valley for this unashamedly multi disciplinary meeting. The location in Tours was particularly appropriate, since it is near to the final resting place of that archetypal multidisciplinarian, Leonardo da Vinci, whose memory it celebrates as an honorary son of the city. The glossy and well-appointed Congress Centre Vinci, in which the conference took place, exemplifies this continuing homage.

A core aim of the COST 825 action has been to bring together the different scientific traditions which, while sharing an interest in mammary gland biology, have historically remained separate and even remote from one another. The medical (breast cancer) and the agricultural (lactation and animal production) traditions represent the extremes of this separation. The eight sessions of the conference, most with six invited speakers, complemented by 64 posters, picked out key areas across this multi disciplinary spectrum of mammary gland biology.

# Cell-cell interactions in mammary cancer

A strong undercurrent of mammary cell culture technology ran through this session. Catherine Niemann, (reporting on work at the Max Delbrueck Center for Molecular Medicine, Berlin, Germany) used a cell-line, EpH4, cultured on matrigel to demonstrate distinct morphogenic programmes provoked by hepatocyte growth factor and neuregulin, and transduced via independent receptor kinase pathways. Jesus Soriano (University of Geneva Medical School, Switzerland) discussed the ability of oncogenes and tumour suppressors to modify the growth characteristics of TAC-2 cells on plastic and in collagen gels. Clive Dickson (Imperial Cancer Research Fund, London, UK) combined targeted transgene

technology with transplantation into cleared mammary fat pads to uncover requirements for fibroblast growth factor (FGF)-receptor and cyclin D1 in overlapping but different aspects of mammary growth and differentiation. Paul Edwards (Department of Pathology, Cambridge, UK) further expounded on his elegant techniques of mammary transplantation, while Michael O' Hare (University College, London, UK) also concentrated on the harnessing of technologies - automated cell separation and proteome analysis - in high throughput approaches to studying cells from normal breast and breast cancer.

# Immunology of the mammary gland

A major focus of this session was mastitis and its control. This is not an obvious topic of immediate interest to readers of *Breast Cancer Research*. However, a presentation on the modulation of immune reactions during normal mammary function (Karin Persson Waller, Swedish University of Agricultural Science, Uppsala, Sweden) and one on immune surveillance in the bovine mammary gland (Max Paape, USDA-ARS, Beltsville, USA) together with information from other speakers (Céline Riollet and Henri Salmon, INRA, Nouzilly, France; Guilia Giovannini, University of Milan, Italy; Hilde Dosogne, University of Gent, Belgium; James Leigh, Institute of Animal Health, Compton, UK) on cell movements within the mammary gland and inflammation-associated tissue remodelling, suggested oblique clues to cellular processes (early surveillance and killing; metastatic dispersion) in breast cancer.

# Mammary gland development

There is no serious dispute that an understanding of normal mammary gland development will complement and, in some cases underpin, understanding of the development of breast cancer. The full programme of mammary development from pre-pubertal growth (Stig Purup, Danish Institute of Agricultural Science, Tjele, Denmark) to lactogenesis (Jean Djiane, INRA, Jouy-en-Josas, France) was explored. The roles of different cytokines and growth factors were related to their tissue and cellular localisation (Fred Sinowatz, University of Munich, Germany), to their cognate binding proteins (IGFBP-5; David Flint, Hannah Research Institute, Ayr, Scotland) and ultimately to the transcriptional regulators that are the molecular destinations of many of their signalling pathways (STAT 5; Lothar Henninghausen, NIH, Bethesda, USA).

# Signal transduction in mammary cancer

Two speakers from the University of Utrecht, The Netherlands, stressed the concept of the mammary gland as an endocrine organ. Rien Blankenstein focussed on the biosynthesis of oestrogen in normal breast and in breast cancers while Jan Mol described the progesterone-induced synthesis of growth hormone and the local and (at least in the dog) systemic consequences of that synthesis. It would be

stretching a point to extend this endocrine concept to the production of opioid casomorphine peptides by the lactating breast, although, as Elais Castanas (University of Crete, Heraklion, Greece) described, opioid receptors in breast do respond to such peptides and other opioid agonists and that a common element of this response is a diminution in cell proliferation. Gerald Cunha (University of California, San Francisco, USA) and William Muller (University of Hamilton, Ontario, Canada) both described the use of knockout mice (involving growth factors and growth factor receptors, respectively) in dissecting the roles of individual growth factors and consortia of growth factors in the establishment of hyperplasia and the induction of cancer.

# Cellular mechanisms in mammary signalling pathways

A comprehensive treatment of signalling pathways could have taken up several meetings. The speakers in this session offered a snapshot of some 'hot-spots'. Dave Fernig (University of Liverpool, UK) described the roles of heparan sulphate components of cell surface and extracellular matrix proteins as modulators of growth factor action on mammary cells and developed the concept of dual-receptor systems (heparan sulphate-glycoprotein plus classical cognate receptor) and their ability to diversify responses and outcomes to growth factor challenge. A parallel theme of cell-surface/intracellular matrix interactions was developed by Marisa Faraldo (Institut Curie, Paris, France). These interactions can be mediated by integrins and Faraldo described the use of a mammary-targeted dominant negative b-integrin transgene in mice to define the signalling roles of b1-integrin in mammary gland development and differentiated function. Knockouts were prominent in Paul Kelly's presentation (INSERM, Paris, France) of the pleitropic effects of the prolacin receptor-null phenotype. A new dimension was added to our understanding of the mechanism of the intracellular somatolactogenic actions of prolactin by Charles Clevenger (University of Pennsylvania Medical Center, Philadelphia, USA) with his demonstration of interaction between Prl and a partner protein that ensures its translocation to the nucleus. As in other cells, different signals are transduced by different enzymes at the termini of their signalling pathways in mammary epithelia. In the case of apoptotic signals, Andreas Marti (University of Bern, Switzerland) described the involvement of caspases. In functionally differentiated mammary cells, Roger Clegg (Hannah Research Institute, Ayr, Scotland) described the involvement of targeted cAMP-dependent protein kinase as a tonic regulator of the constitutive pathway for casein secretion.

# Manipulation of milk composition

Influences of both the nutritional status of the lactating subject (Henri Rulquin, INRA, Rennes, France; Dale Bauman, Cornell University, Ithaca, USA; Giuseppe Bertoni, Instituto di Zootecnica, Piacenza, Italy) and the patho-physiological status of the mammary gland (Jurg Blum, University of Bern, Switzerland; Ioannis Politis, Delta Dairy spa, Athens, Greece) on milk composition were described. The roles of genetic modification and naturally-occurring polymorphisms in the setting a

priori of quantitative limits to the nutritional modulation of composition (Juan Medrano, University of California, Davies, USA; Peter Dovc, University of Ljubljana, Domzale, Slovenia), suggested parallels with the involvement of genetic background in determining predisposition to breast cancer development.

# Transcription factors and gene expression in the mammary gland

By this stage in the meeting, that sensation of hearing the same melody, but in a different key and/or arrangement was beginning to happen. The extracellular matrix was again highlighted, this time by Charles Streuli (University of Manchester, UK), and in its role as a modulator of epithelial cell-specific transcription in mammary tissue. A further aspect of the apocrine function of mammary epithelia, in the expression of different isoforms of NF1, was described by Finian Martin (University College, Dublin, Ireland). STATs featured again, both as 'death' signals in mammary apoptosis (Christine Watson, University of Cambridge, UK) and as modulators of casein gene expression, together with NF-kB and glucocorticoids, as described by Wolfgang Doppler (University of Innsbruck, Austria). Presenting work done while he was at Monash University (Melbourne, Australia), Ross Thomas (Imperial Cancer Research Fund, London, UK) discussed the importance of the ELF groups of transcription factors in normal mammary cell growth and differentiated function. Yvan de Launoit (Institut Pasteur, Lille, France) stressed the roles of the related PEA3 group of transcription factors in tumorigenesis.

# Steroid receptors, chromatin and co-activators

Hinrich Gronemeyer (Strasbourg, France) gave a lucid overview of current concepts governing our understanding of the structural interactions between the ligand binding domain of nuclear receptors and their cognate ligands. Bruce Whitelaw (Roslin Institute, Edinburgh, Scotland), Trevor Archer (University of Western Ontario, London, Ontario, Canada) and Luciano Di Croche (University of Marburg, Germany) addressed different aspects of a single question: What influence does the supramolecular organization of DNA into chromatin have over the modulation of gene expression, and how plastic is this organization? All came up with related answers in the areas of nucleosome organization and chromatin remodelling.

# Postscript

It seems appropriate that readers should be left to 'cherry-pick' their own conclusions from this abundant diversity of information and experimental approach.

Moves are in progress to ensure the continuation of the European Mammary Gland Biology Network beyond June 2000. Further information on the current COST Action 825 can be found at http://cost825.med.uoc.gr.