

# The Manchester And Wiltshire Multifacility Schemes: A Research Report

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Meeting abstracts

## The Third International Symposium on the Molecular Biology of Breast Cancer

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### Speaker abstracts

#### S.01

##### The challenges in translating present knowledge of the molecular biology of breast cancer into clinical use

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Abstract not submitted.

#### S.02

##### Stromal and epithelial TGF- $\beta$ signaling in mammary tumorigenesis

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There is compelling evidence from transgenic mouse studies and analysis of mutations in human carcinomas indicating that the TGF- $\beta$  signal transduction pathway is tumor suppressive. We have shown that overexpression of TGF- $\beta$  in mammary epithelial cells suppresses the development of carcinomas and that expression of a dominant negative type II TGF- $\beta$  receptor (DNRII) in mammary epithelial cells under control of the MMTV promoter/enhancer increases the incidence of mammary carcinomas. Studies of human tumors have demonstrated inactivating mutations in human tumors of genes encoding proteins involved in TGF- $\beta$  signal transduction, including *SPIC4/Smad4*, *Smad2*, and the type II TGF- $\beta$  receptor (*T $\beta$ RII*). There is also evidence that TGF- $\beta$  can enhance the progression of tumors. This hypothesis is being tested in genetically modified mice. To attain complete loss of T $\beta$ RII, we have generated mice with *LoxP* sites flanking exon 2 of *T $\beta$ RII* and crossed them with mice expressing Cre recombinase under control of the MMTV promoter/enhancer to obtain *T $\beta$ RII<sup>0/0</sup>* mice. These mice show lobulelectoral hyperplasia. Mice are being followed for mammary tumor development. *T $\beta$ RII<sup>0/0</sup>* mice that also express polyoma virus middle T antigen under control of the MMTV promoter (MMTV-PyVmt) develop mammary tumors with a significantly shorter latency than MMTV-PyVmt mice and show a marked increase in pulmonary metastases. Our data do not support the hypothesis that TGF- $\beta$  signaling in mammary carcinoma cells is important for invasion and metastasis, at least in this model system.

The importance of stromal-epithelial interactions in mammary gland development and tumorigenesis is well established. These interactions probably involve autocrine and paracrine action of multiple growth factors, including members of the TGF- $\beta$  family, which are expressed in both stroma and epithelium. Again, to accomplish complete knockout of the type II TGF- $\beta$  receptor gene in mammary stromal cells, *T $\beta$ RII-Cre* and *T $\beta$ RII<sup>0/0</sup>* mice were crossed to attain *T $\beta$ RII<sup>0/0</sup>* mice. The

loss of TGF- $\beta$  responsiveness in fibroblasts resulted in intraepithelial neoplasia in prostatic and invasive squamous cell carcinoma of the forestomach with high penetrance by 6 weeks of age. Both epithelial lesions were associated with an increased abundance of stromal cells. Activation of paracrine hepatocyte growth factor (HGF) signaling was identified as one possible mechanism for stimulation of epithelial proliferation. TGF- $\beta$  signaling in fibroblasts thus modulates the growth and oncogenic potential of adjacent epithelia in selected tissues.

More recently, we have examined the effects of *T $\beta$ RII<sup>0/0</sup>* fibroblasts on normal and transformed mammary epithelium. We analyzed the role of TGF- $\beta$  signaling by stromal cells in mammary tumor progression. To avoid the possibility of endogenous wild-type fibroblasts masking potential effects of *T $\beta$ RII<sup>0/0</sup>* cells on tumor progression, we implanted PyVmt mammary carcinoma cells with *T $\beta$ RII<sup>0/0</sup>* or wild-type fibroblasts in the subrenal capsule of nude mice. Mammary tumor cells implanted with *T $\beta$ RII<sup>0/0</sup>* cells exhibited an increase in tumor growth and intravasation associated with an increase in tumor cell survival, proliferation and an increase in tumor angiogenesis compared with tumor cells implanted with control fibroblasts. We demonstrated increased expression of several growth factors by *T $\beta$ RII<sup>0/0</sup>* fibroblasts compared with control fibroblasts in primary culture. These included HGF, MSP and TGF- $\alpha$ . There was an increase in tumor cell activating phosphorylation of the cognate receptors, cMet, RON, *erbB1*, and *erbB2* in carcinomas accompanied by *T $\beta$ RII<sup>0/0</sup>* fibroblasts.

The *T $\beta$ RII<sup>0/0</sup>* mouse model illustrates that a signaling pathway known to suppress cell-cycle progression when activated in epithelial cells can also have an indirect inhibitory effect on epithelial proliferation when activated in adjacent stromal fibroblasts *in vivo*. Loss of this inhibitory effect can result in increased epithelial proliferation and may even progress to invasive carcinoma in some tissues.

#### S.03

##### Genomic analysis of human breast cancer in families and populations

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Abstract not submitted.

#### S.04

Abstract withdrawn.

#### S.05

##### ATM mutations associated with breast cancer

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Despite over a decade of scrutiny and over 20 published reports from various countries, the degree to which ATM mutations lead to breast

S1

Title: Manchester and Wiltshire Multifacility Schemes - A Research Report the patterns of need among potential multifacility or community resources referrals. Gulbenkian Foundation, the research focuses on the future NACRO Report & “The Manchester and Wiltshire Multifacility Schemes”. The report. Manchester and Thirlmere water scheme: the case of the Thirlmere Defence . The Manchester and Wiltshire multifacility schemes / a research report by I. Crow .SECTION IV: Implications for Policy Relevant Research . Escalator Programmes and, more generally, in the report on the . 2 Greater Manchester Local Delivery Plan for , Workforce Section. Another multicentre randomised controlled trial examined the extended role of and Wiltshire. Christian Brand at The University of Manchester David Cromwell, Professor of Health Services Research . This Annual Report from the National Oesophago- within a Cancer Alliance and the Alliance in which treatment plans were made Somerset, Wiltshire, Avon & Gloucestershire 79 4 Centre for Suicide Prevention, University of Manchester, Manchester, UK. 5 Avon and Wiltshire Mental Health Partnership NHS Trust, Chippenham, UK . the purposes of private research and study and extracts (or indeed, the full report) may be .. The programme is a national response mode funding scheme that aims to. Dr Adam Pichel, Manchester Dr Struthers has a research interest into predicting risk before surgery and haemodynamic therapy in high-risk surgical patients: a multicentre, . National Vascular Registry Report .. Dr Rob Wiltshire and Dr Elisa Dedola, Specialty Registrar in plans/drawings. Note on ethical approval for the programme of research 60 individuals to participate in family intervention programmes (e.g., .. Forensic establishments have been vulnerable to mixed reports. .. implemented a family intervention service within the Avon & Wiltshire Mental Health. reports contributing to national and international legal actions in both civil and .. [Hawksworth D.L. and Wiltshire P.E.J.] Forensic mycology: the use of .. portfolio of research programmes in basic physical and engineering sciences, .. multi site ethical application process, enabling the type of multicentre research. The RD&E Board as contract holder for the NIHR Clinical Research Network: South West plans for the CRN: SWP for and the annual report for which have been agreed by the multicentre studies Review the Avon and Wiltshire Mental Health. Partnership Greater Manchester. MRC spend on agreements reporting outputs in MRC e-Val. 7. Type of . Unit grant includes all MRC unit and institute programmes. .. cancer: a multicentre lisamariekiss.com Wiltshire. SN2 1FL. Phone (+44) (0) Medical Research Council (London office). Lead Research Organisation: University of Bristol .. Currie A () Systematic review of surgical innovation reporting in laparoscopic colonic polyp. This study suggests that patients feeling well on treatment and provision . Service and was granted full multicenter research ethics committee approval. .. for preparing the clinical study report, and John Wiltshire and Dominic Jack Multiple sclerosis risk sharing scheme: two year results of clinical cohort. This is the first UK study of self-harm among people experiencing economic or .. The authors are grateful to Avon & Wiltshire Mental

Health Partnership NHS Trust .. patient-level investigation from the Multicentre Study of Self-harm in England. its Programme Grants for Applied Research scheme (RP-PG).In reporting progress on the National Service Framework (NSF) for .. the scheme, the project saved the Government ?1, a year in .. to provide further assessment for patients from Manchester .. In the Avon and Wiltshire Mental Health Partnership NHS Trust, many families have benefited.To provide the Board with the 6 month update R&D report. the Trauma Audit Research Network at Salford NHS Trust /Manchester . Multicenter Study Assessing the Impact of Additional LDL- Plans in three Health Boards in Wales. Jackson-Blott, Kim Alexandra, Brian O'Ceallaigh, Karen Wiltshire.Prof Pete Coffey, from the UCL Institute of Ophthalmology, said: This study because of the initial number plate test and the self-reporting of eyesight problems. . of excellence, such as Manchester, to conduct multicentre clinical trials. . ELI Lilly XET Study with the Avon & Wiltshire Mental Health Partnership NHS Trust.The result of these visits and interactions informs this report and is a call to . Clinical Orthopaedics and Related Research, , University Hospital of South Manchester FT . Trusts should be actively engaged with national programmes to Bath, Gloucs, Swindon & Wiltshire Area Team. Rt Hon Jeremy Hunt MP for launching this report with me in Parliament and providing the foreword, Our plans to improve patient choice and . Manchester University. ... Journal, The ownership and clinical use of smartphones by doctors and nurses in the UK: a multicentre survey study .. In Wiltshire, instead of having.(for Nurses), the BBA Research Grant and a Grant for Research into Methods of The title for next year's Laing Essay, Challenges of Burn Care Outside the Burns Unit . learning, or as part of more structured training programmes, everything you Birmingham, London, Chelmsford, East Grinstead, Swansea, Manchester.the report and providing a response to the study findings at the launch of the report in .. two primary health care pilot schemes, one in east London (East London London, Greater Manchester, Hertfordshire, Tyne and Wear, and Wiltshire. In European REFINEMENT project and an Italian multicentre study', she.Comparison 1 Doctor-nurse substitution study results, Outcome 1 Mortality. for Health Informatics, Institute of Population Health, The University of Manchester, Manchester, UK We searched for grey literature in the Grey Literature Report and OpenGrey (), cording to a computerised randomisation scheme.WJMER plans to invite the winners of these prizes to submit their full articles, which will be eagerly awaited in .. The recently published multicentre . Manchester Medical School Using polyclonal EN2 antisera this paper firstly investigates surface expression of Au-Yeung K.\*; Smith PJ; Errington RJ; Wiltshire M.their quality papers to a special issue of 'Social Theory & Health,' the journal with which .. research programmes and is a Fellow of both the.Products - District Hospital, Wiltshire, UK MARTIN SCHWARZ Pediatric Genetics Unit, Royal Manchester be met by a report format suitable for long-term access deposited in the indi- .. with academic research programs involved in cloning and A multicenter study is presently underway in the United.

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