

Dr Germaine Caldwell PhD

Postdoctoral Fellow

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School of Cancer Sciences

About

Germaine Caldwell is a Postdoctoral Fellow in the School of Cancer Sciences.

Germaine has published a number of research papers in scientific journals in the field of colorectal cancer research and human molecular genetics. She has received grants from the Wellcome trust VIP award, core/Belmont trust and UHB Charities.

She has presented her work to a range of audiences both nationally and internationally.

Qualifications

- PhD in Molecular Genetics, University of Birmingham, 1998
- BSc (Hons) in Biological Sciences, University of Plymouth, 1992

Biography

Germaine Caldwell qualified with a BSc (Hons) in Biological Sciences from the University of Plymouth in 1992. She went on to study for a PhD in Molecular Genetics at the University of Birmingham.

Following her PhD Germaine worked at Roswell Park Cancer Institute (America's first cancer centre) in Buffalo USA. During her time at Roswell Germaine studied two disorders associated with sight and hearing loss in affected individuals (Usher's syndrome and Best's vitelliform macular dystrophy).

She returned to the University of Birmingham in 2000. Since that time she has studied the role of Wnt signalling in colorectal tumourigenesis initially in the department of surgery (Medical School) and more recently in the School of Cancer Sciences. Since 2007 she has been studying the epigenetic changes involved in the development of colitis-associated colorectal cancer in patients with ulcerative colitis (UC). Through her work on cancer and inflammatory bowel disease (IBD) Germaine collaborates with a number of clinicians across the West Midlands. Since 2007 she has received grants to carry out the UC-related work from a number of funders including core and UHB Charities.

Research

Research Themes

Colorectal Cancer Cell Biology, Epigenetics, Methylation, Biomarker development, Clinical Trials.

Colorectal Tumourigenesis

The main emphasis of Germaine's research over the last 11 years has been to study the role of the Wnt antagonists in the development of colorectal neoplasia. The work has analysed the expression of a number of Wnt-related genes in tumour and normal colon mucosa taken from patients with sporadic colorectal cancer and patients with the genetic form of the disease, familial adenomatous polyposis (FAP).

The Wnt antagonist sFRP1 is silenced at the early stages of colorectal tumourigenesis. Subsequent work has shown that other Wnt antagonists (sFRP2, sFRP4, sFRP5 and WIF1) are also silenced. Analysis of the mechanism for gene silencing has shown that the sFRP1 gene is hypermethylated in tumours compared with normal mucosa.

More recently the work has examined the role of the Wnt antagonists in colitis-associated colorectal tumourigenesis. Ulcerative colitis affects around 120,000 people in the UK. Patients with UC have an increased risk of developing colorectal cancer with an actuarial cumulative incidence by disease duration of 1.5% at 10 years, 7.7% at 20 years, 15.8% at 30 years, and 22.7% at 40 years. Cancer risk is also associated with extent of disease.

Guidelines suggest all patients with UC have an index colonoscopy approximately 10 years after the onset of colitic symptoms. Surveillance colonoscopies are subsequently conducted yearly, 3-yearly or 5-yearly dependent on all the variables. Despite the surveillance in high-risk patients, colonoscopy is not wholly effective in cancer prevention. There is a pressing clinical need for a supplementary test that would improve our ability to identify patients for surgery, prior to the onset of invasive cancer. In addition, more effective risk stratification would reduce surveillance frequency for a lower risk population.

We have demonstrated hypermethylation of the Wnt antagonists (sFRP1 and WIF-1) in UC-associated dysplasia and cancer. Methylation of these markers was also detected in macroscopically normal mucosa taken from patients with UC-associated neoplasia suggesting a field change. Data sFRP1 and WIF1 demonstrates hypermethylation of one or more CpG sites occurs in 77% of colitis-associated cancer, 72% of colitis-associated dysplasia and 56% of non-neoplastic tissue from patients with colitis-associated cancer. None of controls (UC patients without neoplasia and disease <10years) was methylated at these 4 CpG sites. The data indicates a sensitivity of 76% and a specificity of 100% at detecting colitis-associated neoplasia (cancer and dysplasia). This work is continuing and a panel of predictive markers is being developed to improve sensitivity.

In addition to providing biomarkers of progression, this also raises the potential for using therapies directed against these events to delay or prevent tumour formation. The panel of predictive markers may provide useful surrogate markers of effect in future clinical trials of novel treatment agents. Currently samples from small phase II clinical trial are being tested. The trial assesses the effect of glucocorticoid steroids on methylation and expression of the Wnt antagonists in the UC population. Cell line data suggests that these steroids can reverse the expression of the antagonists and may have an effect on tumour prevention.

Publications

K. J. Leong, W. Wei, L. A. Tannahill, G. M. Caldwell, C. E. Jones, D. G. Morton, G. M. Matthews, S. P. Bach. Methylation profiling of rectal cancer identifies novel markers of early-stage disease. *British Journal of Surgery* 2011; 98: In Press

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