Pergamon

European Journal of Cancer Vol. 33, No. 9, pp 1521–1526, 1997

Printed in Great Britain.
0959-8049/97 $17.00+0.00

International Cancer News

Compiled by Helen Saul

From the Globe

Breast Cancer Test Awarded Licence

A test for the second breast cancer gene has been granted a worldwide licence by the American and British institutes where researchers discovered BRCA2. The gene was isolated by scientists working at Duke University in North Carolina, U.S.A. and at the Cancer Research Campaign (CRC) in the U.K.

The patent application on the gene is still pending but in the meantime, CRC Technology and Duke University have awarded the licence to U.S.A.-based genetic testing company, OncorMed. The British National Health Service has been given a free licence to test for BRCA2, and Duke University will be able to continue testing.

Under the agreement, the test will only be available where patients have access to specialised genetic and psychological counselling. No mail order service will be allowed.

Dr Mike Stratton at the Institute of Cancer Research in London and Dr Andy Futreal at Duke University lead teams of scientists who discovered that abnormalities in the BRCA2 gene increase risk of breast and ovarian cancer. Between 5 and 10 % of all breast cancer is thought to be inherited and abnormalities in BRCA2 account for more than a third of families with inherited breast cancer. The BRCA1 gene, responsible for a similar proportion, was previously patented by the University of Utah and Myriad Genetics.

The Cancer Research Campaign has previously opposed the patenting of genes and Professor Gordon McVie, Director General, said CRC had not changed its position. 'Nothing has changed our mind. We have taken a pragmatic position. We are patenting this gene now because we can't go back and patent it later. But there should be a public debate.' Professor McVie said he found the idea of patenting human genes 'a bit distasteful' but he said that when CRC, which is a charity, asked its supporters for their opinion, it found that all were in favour of patenting.

In the U.S.A., Dr Leslie Alexandre at OncorMed said that genetic testing for breast cancer remained controversial and she stressed the importance of pre- and post-test counselling and of informed consent. She said it is impossible to separate genetic information from other medical information. 'Our height, weight, blood pressure and cholesterol levels all have an heriditary component,' she said.

Inheriting a mutation in one of the breast cancer genes greatly increases the risk of breast and ovarian cancer, she said, but not to 100 %. 'Most people feel there is something they can do. Even if it means simply being more diligent and starting screening earlier than they otherwise would have done. Some people may go for prophylactic surgery, which doesn't guarantee they will never get cancer but it probably significantly reduces the risk. Others may want to change their diet or change their lifestyle,' she said.

Earlier this year, the benefits and risks of prophylactic surgery were discussed at the annual meeting of the American Association for Cancer Research. Results from a study at the Mayo Clinic in Rochester were presented. The records of women at high risk for breast cancer were analysed retrospectively and researchers found that women who had a bilateral prophylactic mastectomy had a 91% reduction in their risk of breast cancer. However, oncologist Dr Lynn Hartmann stressed that these findings should not be taken as a universal recommendation to have prophylactic mastectomy.

Dr Judy Ellen Garber of the Dana-Farber Cancer Institute in Boston said that women who had mastectomies were not universally happy with them. Women who chose not to have surgery would be able to take advantage of emerging medical alternatives, she said. These include chemo- and bioprevention and trials are already underway.

Synthesis of New Cytotoxic Agents

Scientists in the U.S.A. have synthesised a new class of anti-cancer drugs, known as epothilones. These compounds work in the same way as taxol but have a simpler structure which allows synthetic chemists to make analogues more easily. Several teams of American scientists have now reported successful chemical syntheses of various epothilones and a Californian group recently published work which may pave the way for the creation of combinational libraries of molecules for biological screening. Epothilones are produced naturally by a cultured strain of the myxobacterium Sorangium cellulosum.

Many anti-cancer agents work by inhibiting microtubule assembly but the epothilones, like taxol, kill cells by inhibiting the disassembly of microtubules. The Californian group, at Scripps Research Institute, La Jolla, is led by Professor K.C. Nicolaou. His team used solid-state chemistry to synthesise epothilone A,

a process commonly used by the pharmaceutical industry to produce combinatorial libraries. The Scripps group, though, was the first to use it to produce a complex natural product.

Comparison of various epothilone analogues will allow chemists and biologists to explore the molecule and find out which features of the compound are essential for its anti-cancer activity. Early *in-vitro* studies have suggested that epothilones may make better drugs than taxol as they appear to be active against some taxol-resistant cancer cell lines

However, the toxicity of these compounds has yet to be explored and the production of drugs based on this work remains a distant prospect.

Synthesis of epothilones A and B in solid and solution phase, *Nature*, **387**, 15 May 1997.

New Edition of TMN Classification

The fifth edition of the TNM Classification of Malignant Tumours was published this summer. It is the result of a series of consultative editorial meetings organised and supported by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). The meetings were set up to ensure that there is only one standard and AJCC and UICC now publish identical classifications. According to the authors, changes since the previous edition reflect new data on prognosis as well as new methods for assessing prognosis. The testis tumour classification now incorporates prognostic serum markers into the stage grouping, for example, and may serve as a model of how to use nonanatomic prognostic factors without obscuring the building blocks of TNM. Similarly, the new classification of gestational trophoblastic tumours uses hCG levels and duration of disease to modify the anatomic factors in determining the final stage.

The classification of nasopharyngeal carcinoma has been revised to incorporate the needs of radiotherapists, and changes in the classification of prostate, bladder and kidney tumours reflect advances in urology. A new classification of fallopian tubes has been included.

The TNM Classification of Malignant Tumours, Fifth Edition, is edited by Leslie Sobin, Armed Forces Institute of Pathology, Washington DC and Christian Wittekind, University of Leipzig, Germany. Published by John Wiley & Sons, Inc.

From Europe

ESO College: Building a European Team

At the heart of the College of the European School of Oncology (ESO) is the desire to create and maintain team spirit among cancer specialists throughout Europe. The College relies on its members' enthusiasm, participation and support and aims to spread knowledge and experience in cancer treatment and research.

The College, which is a forum for everyone who has followed an ESO course, promotes communication between professionals from different countries and from the many different specialities which focus on cancer. ESO courses bring together these people with their widely differing views and experience, and allow them to exchange opinions and ideas. Once courses are over, and everyone has returned to his or her normal daily routine, the College exists to build on the links between members, specialities and countries and to allow the learning process to continue.

By offering fellowships and scholarships, the College encourages oncologists to work in different European countries and further the process of pooling resources and capabilites. It is becoming a source of advice and guidance and can provide an active response to the challenges faced by professionals in their day to day practice.

Above all, the College means that its many and diverse members, about 400 in all so far, are no longer alone in facing the cancer's many challenges. They are privileged in being able to work together to develop a vision of the future for cancer research and treatment.

'These are all features which distinguish the College from the traditional form of alumni club,' says Dr George Asimakopoulos, ESO College and Conventions Coordinator. 'It is a dynamic structure like the ESO itself, and one in which every member can take an active part.'

EORTC Data Center Fellows Profile: Laurence Collette

Every statistician's nightmare, says Laurence Collette from the EORTC Data Center in Brussels, is being approached by a doctor who has spent months or even years collecting useless data. And it happens all too often in hospitals and universities where it is normal practice for researchers to collect all their data before consulting the statistician.

'You might find that their sample size is not big enough, or that a bias has crept in. Sometimes they have answered a question all right, but not the one they thought they had asked,' she says. 'After they have collected all the data, there is nothing you can do to help.'

It is for reasons like this that she enjoys working at the EORTC Data Center. Here, she is involved in developing the study from the first idea right through to publication of results. As a biostatistician, her training was in mathematics and statistics and she graduated from Université Catholique de Louvain (UCL), Belgium, before taking a Master of Science in biostatistics at Limburgs Universitair Centrum, Diepenbeek, also in Belgium. But she also tries to learn as much as she can both about the treatment or management strategy being studied and the disease itself.

Ms Collette has been at the EORTC Data Center since March 1995. She has worked on trials of gastro-intestinal cancer, lung cancer and fungal infections. She is currently working on phase II and III clinical trials on cancers of the genito-urinary tract and of the head and neck. She also works within the EORTC Radiotherapy group on genito-urinary tract and breast cancers. Meta-analysis is another of her special interests at EORTC, and she has written statistical methodology papers.

Ms Collette worked previously as an assistant to the professor in the Biometry and Data Analysis Unit at UCL. One of the special features of working at EORTC is that statisticians come from a range of different fields and they can learn from each other, she says. 'Someone might have come from cardiovascular medicine, someone else will have specialised in quality of life studies. We give presentations of models we have used in previous work and of methods and tools we use or even develop in our daily activities. It's a good way of keeping up to date.'

From the Countries

U.K.

HAI Gives Quality of Life for Patients with Colorectal Liver Metastases

Patients with colorectal liver metastases (CLM) may have a better quality of life if they receive chemotherapy via hepatic artery infusion (HAI) rather than systemically, according to researchers at the Imperial College School of Medicine, London.

CLM develop in 40% of patients who have a primary colorectal cancer excised. They are not usually curable and the only treatments which have been shown to significantly prolong survival are systemic fluorouracil/folinic acid and regional fluoxuridine (FUDR).

In the London trial, 135 patients were randomised into three groups. Patients treated for symptom control only were in general more anxious. Those receiving systemic chemotherapy had their quality of life impaired by side-effects compared with patients receiving HAI, who had similar survival rates but better sustained quality of life.

Professor Tim Allen-Mersh, Consultant Surgeon at Chelsea and Westminster Hospital, and a co-author of the study, said that HAI is not widely used in many European countries, including Britain. This is partly because of a lack of persuasive results from previous studies. 'People have taken the view that it doesn't produce a survival benefit compared with systemic chemotherapy,' he said.

This study found a significant benefit in terms of quality of life with HAI. Quality of life is difficult to assess scientifically and questionnaires tend to simplify patients' problems. Professor Allen-Mersh said this has meant it is often not taken sufficiently seriously. He said, 'Measurements may be crude, but they are not vague. We ask patients if they feel sick, or have a sore mouth, whether they can get out and about and if they have stopped having sex. It is not complicated and the results do give added insights.'

Studies examining small differences in survival rates require large numbers of patients to reach statistical significance. But those looking for big differences in quality of life need only fairly low numbers and can be easier to carry out, said Professor Allen-Mersh.

One problem in promoting widespread use of HAI is the shortage of centres where there is both a medical oncologist and a surgeon interested in this technique. In some centres a relatively high rate of complications such as catheter leaks and displacements or occlusions has increased reluctance to use HAI. Another drawback is financial since HAI can cost up to eight times as much as systemic chemotherapy. However, Professor Allen-Mersh said this has to be considered both in the context of cost and benefit. 'If a treatment has a 25 % partial response rate, you spend a lot of money and you are treating 75 out of 100 patients for no benefit, and maybe a lot of side effects.

'I think one way ahead is to select patients who are going to benefit and then use the most beneficial treatment on them. It would give us more directed treatments and better use of resources. Patient selection is an important area which needs to be developed,' said Professor Allen-Mersh.

Sally Earlam *et al*, *Journal of Clinical Oncology* **15**, No 5 (May), 1997 pp. 2022–2029

Intensive Radiotherapy Increases Survival in Lung Cancer

An intensive form of radiotherapy may increase survival for people with non-small-cell lung cancer by up to 50 %, according to the results of a new study. Researchers used a technique called Continuous Hyperfractionated Accelerated Radiotherapy, or CHART, and achieved a 2 year survival rate of 29%, compared with 20% among patients receiving conventional radiotherapy.

Patients receiving current standard radiotherapy for non-small-cell lung cancer received 30 radiotherapy treatments over a 6 week period with no treatment at weekends. CHART used 36 treatments over 12 days; that is, 3 treatments a day with no break at the weekend. The rationale for the more intense approach was that it might reduce the chances of regrowth of the cancer between sessions.

The study, which included 563 patients, was co-ordinated by Dr Mahesh Parmar from the Medical Research Council's Cancer Trials Office in Cambridge. He said the two treatments showed little difference in toxicity. Patients receiving CHART had more difficulty swallowing initially, but at 3 months the level of side-effects was the same in both groups.

He acknowledged that CHART cost more than conventional radiotherapy but said that the results of an economic study, carried out alongside his own, will be published soon. ♦♦♦

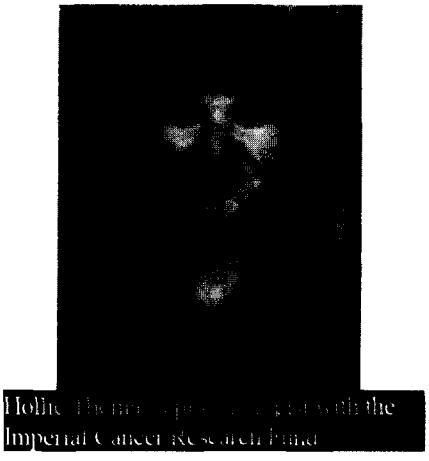
Oestradiol 'Increases Breast Cancer Risk in Post-menopausal Women'

Post-menopausal women with high levels of oestradiol may have an increased risk of developing breast cancer, according to a prospective study in Guernsey. Researchers took blood samples from 2,500 post-menopausal women between 1977 and 1990. More than 60 of the women went on to develop breast cancer, on average 7.8 years after the blood was collected.

The one-third of women with the highest oestradiol levels were five times more likely to develop breast cancer than those in the third with the lowest levels. Levels of testosterone and sex hormone-binding globulin (SHBG) were not linked independently with breast cancer risk.

Hollie Thomas, epidemiologist with the Imperial Cancer Research Fund, was the principle author of the study. She said that oestrogens have been associated with breast cancer for 30 years but that this link has not always been taken seriously because some results have been inconsistent. 'Good large prospective studies help to clarify previous findings. People are coming round to thinking that oestrogens are strongly linked to the risk of breast cancer in post-menopausal women.'

Thomas said that the finding is not yet strong enough to change clinical practice or to suggest a mass screening programme. However, she said that post-menopausal



Hollie Thomas, epidemiologist with the Imperial Cancer Research Fund

women who are obese might be advised to lose weight since obesity is linked with increased levels of oestradiol. It is also helpful for researchers trying to intervene with hormone levels, using drugs such as tamoxifen, for treatment and prevention of breast cancer.

'A prospective study of endogenous serum hormone concentrations and breast cancer risk in post-menopausal women on the island of Guernsey', HV Thomas *et al*, *British Journal of Cancer* **76**, issue 3, 1997.

♦♦♦ CHART was developed at the Mount Vernon Hospital in Middlesex and has been used there since 1985. It is being adopted by other centres involved in the study and an American trial has been set up to test CHART against standard treatments in the U.S.A.

Not every cancer will react in the same way to more intensive radiotherapy, says Dr Parmar. 'Head and neck cancers haven't shown such promising results. We don't fully know why. We don't know what is special about non-small-cell lung cancer.'

However, Dr Parmar, who has worked with CHART for 10 years believes that if it were to become the standard treatment for non-small-cell lung cancer, it could prolong the lives of thousands of people with this poor prognosis disease. 'The most important thing about this study is that people can not ignore these results,' he said. 'The role of CHART should be the subject of intense discussion in lung cancer clinics right round the world.'

'A randomised multicentre trial of CHART versus conventional radiotherapy in non-small-cell lung cancer', M Saunders *et al*, *The Lancet* July 19th, 1997.

DENMARK

Pregnancy Safe After Breast Cancer

Women who have been treated for breast cancer should not be advised to avoid pregnancy afterwards, according to researchers in Denmark. An extensive study of women with primary breast cancer found no evidence that pregnancy could reduce their chances of survival.

Reseachers from the Danish Epidemiology Science Centre, Copenhagen, obtained data on 5725 Danish women with primary breast cancer who were aged up to 45 years old. Details of the women's reproductive histories were taken from national registries and the women were followed up for 35,067 patient-years. Those who had a full-term pregnancy after breast cancer treatment had a non-significantly reduced risk of death compared to other women of similar age, stage of disease and reproductive history before diagnosis.

Several hormones such as oestrogen which are present in high concentrations during pregnancy, are known to encourage the growth of breast tissue. This observation has prompted much discussion about whether women should be advised aganst becoming pregnant after breast cancer treatment. Reproductive factors such as age at first birth and time since the latest birth have been shown to have a prognostic effect, but this was adjusted for in the analysis.

The researchers concluded that pregnancy after breast cancer treatment does not have a negative effect on the woman's survival.

'Should women be advised against pregnancy after breast-cancer treatment?', *The Lancet* **350**, August 2, 1997, pp. 319–322.

APPOINTMENTS

Six New Slots in Manchester

Signatories of an agreement which should attract six cancer experts to Manchester, U.K. from early 1998. The Cancer Research Campaign is funding the new appointments, which are based at the Paterson Institute laboratories at the Christie Hospital and include teaching at UMIST. From left to right: Professor Tony Whetton, Director of the Leukaemia Research Fund Unit, UMIST; Professor Michael Dexter, Director of the Paterson Institute; Trevor Hince, Scientific Director, CRC; Professor Bob Boucher, Prinipal and Vice-Chancellor, UMIST; Professor Robin Procter, Pro-Vice-Chancellor, UMIST; Professor Gordon McVie, Director General, CRC.

New Faces At FECS

The Federation of European Cancer Societies (FECS) decided on its next president, secretary and treasurer in elections in June. Professor Dieter Hossfeld is the President-elect, Dr Michael Price will become Secretary, and Professor Harry Bartelink, Treasurer.

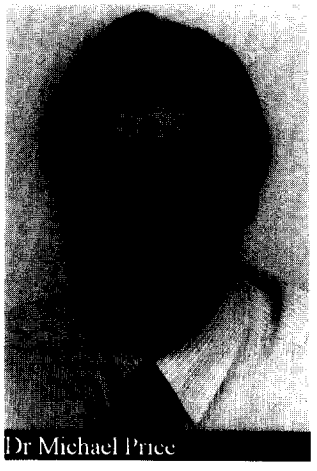
Professor Hossfeld, who is professor of internal medical oncology and haematology at the Medical University Clinic in Hamburg, will take over as president in two years' time. He said that his job would be to pull together FECS' member organisations so that they work in a constructive and productive way. 'Cancer is a multidisciplinary problem and for the sake of our patients, it is an absolute must that all the different disciplines work together as closely as possible.'

Co-operation must extend beyond the medical profession, said Professor Hossfeld. 'This is a political role. Cancer is one of the main killers not only in Europe but also in the rest of the world. We have to have politicians on our side in the fight against cancer.'

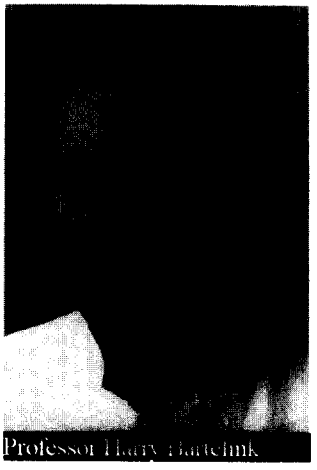
Professor Hossfeld is an adviser to the German and Swiss governments, the German Research Society and the German Cancer Foundation. He is a member of councils of EORTC, UICC and the German Society for Haematology and Oncology. His research activities include molecular and classical tumour cytogenetics, pharmacology and metabolism of anticancer drugs, clinical implications of multidrug resistance and phase II studies in breast, lung and colorectal cancers and soft tissue sarcomas.

Dr Michael Price is the Cancer Research Campaign reader in pharmaceutical sciences at the Department of Pharmaceutical Sciences, University of Nottingham.

Professor Dieter Hossfield



Dr Michael Price



Professor Harry Bartelink

He is currently Secretary General of the European Association for Cancer Research and has served on a number of FECS' committees and working parties. He has also held formal positions with the European School of Oncology (ESO), British Association for Cancer Research and the Biochemical Society.

His research relates primarily to the development of monoclonal antibodies and recombinant fragments for the diagnosis and therapy of human tumours, especially those of bladder, breast and ovary.

Professor Harry Bartelink is chairman of the radiotherapy department at the Netherlands Cancer Institute and professor in clinical experimental radiotherapy of the Free University of Amsterdam. He is a former chairman of EORTC's Radiotherapy Cooperative Group and a member of its Scientific Audit Committee. He coordinates CONQUEST within the European Commission's telematics project and is Secretary General of the International Society for Radiation Oncology. He is a member of the *European Journal of Cancer's* editorial board.

Head, neck and breast cancers are the focus of Professor Bartelink's research and he studies the interaction of radiotherapy and chemotherapy in patients with these cancers. More recently he has been using predictive assays to adapt treatment schedules and researching the use of high-dose, high precision radiotherapy.