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Free access to BRCA2 in Europe

Publicly-funded and not-for-profit research laboratories in Europe will have free access to the *BRCA2* gene patent, Cancer Research UK has announced. Laboratories operating for profit, and the pharmaceutical industry, will pay variable fees for licences, according to the intended use.

Dr. Richard Sullivan, Director of Clinical Programmes at Cancer Research UK, said the move, which follows Cancer Research UK's acquisition of the patent in February, 2004, will be widely welcomed. It is a boost for academic *in vitro* work on the gene itself, and *in vivo* work, for example, using tissue samples to gain additional information on the prevalence of *BRCA2*.

Cancer Research UK's patent is based on the discovery in 1995 of the *BRCA2* gene by Prof. Mike Stratton (Institute of Cancer Research, London). This work was funded by the charity. Other Cancer Research UK scientists at University of Cambridge, UK, later unravelled its mechanism of action (*Nature* 2002, **420**, 6913).

The announcement comes hot on the heels of the European Patent Office (EPO)'s decision to revoke the *BRCA1* patent held by Myriad Genetics Inc. (*see EJC News, Eurofile,* 2004, **40,** 14). The patent covered ownership of *BRCA1* and any gene subsequently derived from use of the gene for therapeutic and diagnostic purposes. As it stood, this gave Myriad sole control over diagnostic testing for breast and ovarian cancer. The company has until the end of 2004 to appeal.

Dr. Sullivan said that Cancer Research's acquisition of the *BRCA2* patent was an important principle, but that the field of patenting in genetics was moving on. The single, highly penetrant cancer genes have probably all been found, he said. Current research is focusing on more subtle changes in gene expression, such as the methylation status of genes or patterns of genetic polymorphisms which, together, create the different cancer genotypes.

''We are moving away from the days when people were rushing out to patent large chunks of the genome, with no clue what the function was. The EPO is setting much higher hurdles for assessing novelty and utility'', said Dr. Sullivan.

''Patents will continue to be the lifeblood of commercialisation, with increasing importance in drug discovery and huge growth in diagnostics in the use of predictive biomarkers. This is already happening in 'orphan' areas such as paediatrics; they are using cutting edge cytogenetic strategies to determine whether children will respond to drugs properly, or suffer serious toxicity.

''HIGHER HURDLES ARE SET FOR NOVELTY AND UTILITY''

''Patenting has to deal with this increased complexity, and still be specific. Otherwise granting a broad patent might stifle essential academic research.''

Instructions for obtaining free licences for BRCA2 patents can be found on Cancer Research Technology Limited's website: www.cancertechnology.co.uk/pages/about_download.html

'Benchmark set' for all-cause 60-day mortality

A new benchmark for all-cause 60-day mortality rates in oesophagogastric, pancreatric and colorectal cancers is reported in this issue of EJC (*see page 2230).*

Researchers from Royal Marsden Hospital, Sutton, UK, analysed 1720 patients treated within randomised trials. The all-cause 60-day mortality was strongly influenced by the site of primary disease, being higher for pancreatic cancer (12.9%) and lowest in advanced colorectal cancer (3.4%). There was, predictably, a significantly lower rate for patients receiving adjuvant chemotherapy for colorectal cancer (0.2%).

However, an accompanying editorial (*see page 2190*) points out that, while mortality should not be ignored, ''the safety aspect of treatment should have been carefully assessed and reported before phase III studies are designed and initiated''.

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Formaldehyde 'is carcinogenic'

Formaldehyde has been classified as carcinogenic to humans by a working group of the International Agency for Research on Cancer (IARC), part of the World Health Organization. The classification was made on the basis of new data which increased the overall weight of evidence.

The working group, which was convened by the IARC Monographs Programme, determined that there is now sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans, a rare cancer in developed countries. They also determined a supporting mechanism.

Limited evidence for the role of formaldehyde in cancer of the nasal cavity and paranasal sinuses was found, along with ''strong but not sufficient evidence'' in leukaemia. This meant that epidemiological studies had produced strong evidence, but the available data does not support the identification of a mechanism for the induction of leukaemia.

The Working Group was comprised of 26 scientists from 10 countries, who evaluated evidence on the carcinogenicity of this widely used chemical. Previous evaluations based on the smaller number of studies available at the time had concluded that formaldehyde was probably carcinogenic to humans. New information from studies of persons exposed to formaldehyde has increased the overall weight of the evidence.

Dr. Peter Boyle, IARC Director, said, ''By signalling the degree of evidence for leukaemia and cancer of the nasal cavity and paranasal sinuses, the working group identified areas where further clarification through research is needed. This represents a service to public health''.

Formaldehyde is produced worldwide on a large scale. It is used mainly in the production of resins used as adhesives and binders for wood products, pulp, paper, glasswool and rock wool. It is also used extensively in the production of plastics and coatings, in textile finishing and in the manufacture of industrial chemicals. It is used as a disinfectant and preservative in many applications.

Common sources of exposure include vehicle emissions, particle boards and building materials, carpets, paints and varnishes, tobacco smoke. Levels in outdoor air are generally low but higher levels can be found in the indoor air of homes.

More than one million workers in the European Union have some degree of occupational exposure, according to IARC. Short term exposures to high levels have been reported for embalmers, pathologists and paper workers. Lower levels have been reported during the manufacture of man-made vitreous fibres, abrasives and rubber and in formaldehyde production industries. A variety of levels has been reported in the production of resins and plastics; however, the development of resins that release less formaldehyde, coupled with improved ventilation, has decreased exposure levels in many industrial setting in recent decades.

''ONE MILLION EU WORKERS ARE EXPOSED TO FORMALDEHYDE''

The working group concluded that two glycol ethers (2-butoxyethanol and 1-tert-butoxy-2-propanol) could not be classified as carcinogenic to humans because of the inadequate level of evidence. Further research is needed on these widely used solvents, the group concluded.

Blood test 'could predict colon cancer'

A simple test measuring the variation in the size of red blood cells could provide a useful screening tool for colon cancer, say American researchers (*Cancer Detection and Prevention* 2004, **28**, 37–42). The test, which is a part of the automated complete blood count, ''may help better identify those patients who should be referred for full colonoscopy'', they say.

The team from University of Texas conducted a retrospective study on all 241 cases of newly diagnosed colon cancer between 1996 and 2000. The red cell distribution width (RDW), which measures the variation in the size of red blood cells, was 84% sensitive and 88% specific for right-sided colon cancer.

The rationale for the study was that iron deficient patients have a raised incidence of colonic cancer. Colorectal cancers bleed more than normal colonic mucosa; chronic bleeding depletes iron stores. Further, an elevated RDW usually precedes other abnormalities of the blood count in the development of iron deficiency.

Faecal occult blood tests (FOBT) have been associated with improved survival from colon cancers, but they only detect current bleeding. Only two-thirds of cancers bleed in the course of a week. Potentially, therefore, RDW, which is designed to detect chronic blood loss, could improve the sensitivity of screening for colonic malignancy.

The variability of red blood size increases before overt anaemia. ''An elevated RDW in an otherwise normal blood count is a sensitive and specific indicator of early iron deficiency'', they say.

The researchers stress that their study was retrospective, but say, ''A large prospective trial is warranted to assess the efficacy of using the RDW for colon cancer screening''.

''A blood test is a simple, inexpensive, and readily available tool that provides potential for high rates of patient acceptance and compliance'', they say.

Steps towards an independent ERC

An entirely autonomous European Research Council (ERC) is now looking more likely, following the publication of a European Commission (EC) communication on the future of European research policy. This hands-off approach by the Commission may have been prompted by criticism from the scientific community about earlier proposals for the ERC (*see Eurofile, EJC News* 2004, **40**(7), 917).

The communication says that the ERC alone will be responsible for setting the research agenda and deciding how evaluation should be conducted. Projects will be proposed by researchers on their own initiative, without thematic constraints, on subjects of their choice. Selection will be on the basis of scientific excellence, as assessed by peer review, with no obligation for transnational collaboration. ''The Commission must have no role to play whatsoever in how these things are conducted'', says Dr. Achilleas Mitsos, Director-General of DG Research.

In another move, Professor Bertil Andersson, the new Chief Executive of the European Science Foundation (ESF), has called for discussions about merging the ESF and ERC by the end of the decade. In an interview, Professor Andersson said, ''ESF networks national research councils and promotes collaboration. It pays for activities via contributions from member organisations. Meanwhile, the Commission-funded ERC, which will also fund basic research, should complement the ESF by fostering competition in a 'champion's league' for research''. The future interplay between the organisations should be looked at in Framework 8, he said. ''It is important to ask whether they should merge''.

This suggestion may not be universally welcomed among other members of the European scientific community. Heads of Europe's research councils, EuroHORCs, recently issued a state- ment demanding that the ERC should be run by a board of independent researchers. This is not specifically mentioned in the Commission communication, but neither is it excluded.

The Commission's communication also left open whether the agency should be an executive agency, a Union agency (having more autonomy), or specific structure – for example, a foundation. This is a concern for EuroHORCs, which says, ''The ERC needs a highly professional but lean administrative structure which is guided by a governing body. There must be no institutional representation of scientific or other European bodies or institutions''.

Further, EuroHORCs is unhappy about the administration of funding. The communication says, ''Support should involve a large number of small scale financial operations'', whereas the EuroHORCs' statement asks that ''grants shall be of significant size in order to denote international recognition and cover the full economic cost of research in relation to the institution where it takes place''.

However, most of the principles in the EuroHORCs' statement are compatible with those in the Commission's communication, and the differences are on matters of detail and interpretation. But the Commission is aware that, even with a more placatory style, there will be tough times ahead. Dr. Mitsos says the key question is how to guarantee to both taxpayers and governments that their money is being used appropriately. ''It depends very much on the selection of persons who are going to give credibility assurance, that their objective is the future of science in Europe and nothing else. This is not simple'', he says.

''WE MUST GUARANTEE THAT MONEY IS USED APPROPRIATELY''

National research councils already operate like this. ''When the UK asks a research council to administer a budget on life sciences, the research council is an intermediary between government and researchers'', says Dr. Mitsos. The government trusts this council ''because the selection of persons and the procedures that are installed are such that they can provide these guarantees''.

Neither the ESF nor the Commission expect the differences in standards and R&D spending between member states to create problems. Professor Andersson: ''If a lauded researcher in Sweden receives no funding from the ERC, then that says something about the national funding. Maybe he is a local hero. But if an Estonian researcher gets one project funded, it might say more than if a country that has a strong research base gets 12''.

Dr. Mitsos recognises the concerns. ''I know that people are afraid that it's new and new things suit those who can cope with everything – meaning bigger countries''.

''PEOPLE ARE AFRAID IT WILL SUIT BIGGER COUNTRIES''

''That could be true to a point, but I don't believe that plans for the ERC *a priori* favour some countries over others''.

He denies that the Commission has had a change of heart following criticism of earlier plans. ''What we were keen to do from the beginning was to define the needs of the scientific community and then make the solution fit, rather than setting up an ERC and then deciding afterwards what it should do'', he says.

Dr. Mitsos is optimistic about the possibility of a substantial increase in EU research funding in FP7. ''I think that more and more people now accept the need for the European Union to invest in the future, and investing in the future means investing in research'', he says.

What with this, and the increased emphasis given to research by the new European Constitution, maybe one day soon researchers will be welcoming the Commission as a benefactor rather than an adversary.

Mary Rice
Brussels

New guidelines for anaemic patients

Even moderate levels of anaemia in cancer patients are sufficient to initiate treatment, according to new guidelines by an EORTC Task Force (*see page 2201*). The guidelines recommend that, for adults with solid tumours or haematological malignancies, treatment with erythropoietic proteins should be initiated at haemoglobin (Hb) levels of 90–110 g/l.

Previous recommendations by American Society of Haematologists/ American Society of Clinical Oncologists (ASH/ASCO) put the threshold for treatment with epoetin at Hb levels of less than 100 g/l.

The EORTC guidelines apply to patients receiving chemotherapy and/or radiotherapy and to those with cancer-related anaemia not undergoing either of those treatments. Erythropoietic proteins may be considered even when patients are asymptomatic, to prevent further decline in Hb levels.

The goals of treatment are to improve quality of life and to prevent transfusions. Anaemic patients who respond have a significantly improved quality of life, it states. However, ''There are insufficient data to determine the effect on survival following treatment with erythropoietic proteins in conjunction with chemotherapy or radiotherapy'', the report states.

Erythropoietic proteins are not licensed to prevent anaemia and the report says, ''We do not currently recommend the prophylactic use of erythropoietic proteins to prevent anaemia in patients who have normal Hb values at the start of treatment''.

The importance of the guidelines is highlighted by the European cancer anaemia survey (ECAS), also published in this issue (*EJC* 2004, **40,** 15 REF). This large multinational, prospective survey included patients being treated for all cancers in cancer treatment centres.

Data on more than 14,000 patients showed that, at enrolment, 2 in 5 patients had Hb levels less than 100 g/l; 2 in 3 had these Hb levels at some stage of the 6 months of the study. Less than 2 in 5 were treated for anaemia and the mean Hb level at which treatment was initiated was 97 g/l.

''Optimal management of anaemia appears to be a critical component of cancer treatment'', the report states. Hb levels of between 100 and 119 g/l were the most common recorded, but ''even this level of anaemia had a significant impact on performance status''.

''IMPAIRED FUNCTIONAL STATUS WAS NO GUARANTEE OF TREATMENT''

Impaired functional status ''was no guarantee of treatment for anaemia''.

The impact of anaemia treatment on survival is still in doubt, but the authors state that better management of anaemia would optimise overall patient care and improve quality of life during treatment.

No more breaking hearts

The free-radical scavenger dexrazoxane can decrease or eliminate the long-term damage caused by chemotherapy in children with leukaemia, according to US researchers. ''The drug is targeted at the point of initial exposure'', notes lead author Steven Lipshultz, ''which means that initial injury is prevented rather than cured''. Furthermore, the drug does not seem to diminish the effectiveness of doxorubicin, although these findings were not conclusive.

Steven Lipshultz (Department of Pediatrics, University of Miami School of Medicine, Miami, FL, USA) and colleagues randomly assigned 101 children with newly diagnosed previously untreated acute lympho-blastic leukaemia (ALL) to doxorubicin, and 105 children to doxorubicin and dexrazoxane. Using serum tropinin T as the primary indicator of cardiac injury, the researchers found that the number of children with heart damage was 29% higher in those given doxorubicin alone than in those given doxorubin and dexrazoxane *(N Engl J Med* 2004, **351**, 145–53). ''At the end of 30 weeks only about 20% of children on dexrazoxane and doxorubicin had measurable serum concentrations of troponin T at any point, compared with more than 50% of those on doxorubicin alone'', says Lipshultz.

Chemotherapy drugs, especially anthracyclines, are well known to cause cardiotoxic effects, many of which might not manifest for several years. In July, 2004, Francois Pein (Department of Paediatric Oncology, Institut Gustave Roussy, Villejuif, France) and co-workers reported that after a mean follow-up of 18 years, 39% of children given doxorubicin for solid tumours had a severe cardiac dysfunction or major ventricular-overload conditions (*Br J Cancer* 2004, **91**, 37–44), a finding that Pein attributes to the ''increasing haemodynamic needs associated with factors such as growth and pregnancy''.

Despite their known cardiotoxicity, anthracyclines have been used for more than 30 years, mainly because use of these drugs as part of a multiagent chemotherapy regimen is so effective, curing more than 70% of children. However, ''the price is that at age 30 years, long-term survivors of childhood cancer are eight times more likely to die of heart-related disease than are those who do not have cancer, and this increased risk does not appear to diminish with increasing follow-up'', explains Lipshultz.

In an editorial (*N Engl J Med* 2004, **351**, 20–21), Leontine Kremer and Huib Caron (Emma Children's Hospital, Amsterdam, Netherlands) note that Lipshultz and colleagues' trial is ''an important step toward effective cardioprotection in children'', mainly because ''60% of children with cancer are given anthracyclines, these children have a high risk for clinical heart failure, and survivors of childhood cancer have a long life expectancy'', says Kremer.

But, ''it is too early to advise dexrazoxane for all children on anthracyclines'', cautions Kremer, ''first, the tumour response needs more work".

Anna York

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PODIUM

A model way to study rare diseases

Professor V Hugh Perry, Director of Neuroscience Research at University of Southampton, UK, became interested in Langerhans Cell Histiocytosis (LCH) following an invitation to the Nikolas Symposium in the mid-1990s. Later, he served on the Symposium's Steering Committee for five years. His research interest is inflammation in the CNS and its contribution to neurological disease.

Professor V Hugh Perry

Why were you speaking at a paediatric cancer meeting?

The Nikolas Symposia are a fantastic way of addressing a complex problem. They are think-tanks which bring together a small group of top quality scientists and clinicians to discuss a specific theme associated with this disease. One meeting focused on the neurological consequences of LCH and I was invited to discuss my work on inflammation in the brain.

What makes the Nikolas Symposia special?

They were established in 1987 by Paul and Elizabeth Kontoyannis, whose son Nikolas, has suffered from LCH since 1981. Clinicians and scientists, about 20 at each meeting, gather in a relaxing environment – in Vouliagmeni, Greece, just outside Athens – to give their different perspectives on a specific problem. For me, as a basic scientist, it was a wonderful experience to meet patients and be suddenly exposed to the clinical reality of LCH.

How successful has the approach been?

A rare disease such as LCH is never going to make it on to the radar screen of the big funding agencies. But the Nikolas Symposium can make a difference by getting people involved. The Kontoyannis family have kept the Symposia going and at least several hundred people have now attended. There have been various successes apart from the growing awareness of LCH itself. For example, Dr. Nicole Grois, a paediatric neurologist and Dr. Hans Lassmann, a neuropathologist , both attended Nikolas Symposia and, in part using the network created by the Nikolas Symposia, have gathered brain tissue biopsies taken from children with LCH to generate completely new insights into the neuropathology of LCH.

How does your own work relate to LCH?

I am a basic neuroscientist and became interested in inflammation biology, I work on the role of macrophages and dendritic in multiple sclerosis and in Alzheimer's disease and other neurological diseases. At the Symposia I have been fortunate to meet experts in immunology, cytokine and dendritic cell biology who were looking at similar biological problems, but from a completely different perspective.

Why is LCH such a difficult problem to unravel?

LCH is a disease that lies at the boundary of oncology and inflammation biology, two complex disciplines and thus finding a rationale cure, one of the aims of the Nikolas Symposia, is a major hurdle. LCH is highly variable, it may present just as a skin rash, which can spontaneously resolve but in other cases it takes on a progressive quality involving many organs: lungs, spleen and liver and children still die of it. There is an involvement of the brain, but we do not know, whether Langerhan's cells enter the brain, cause an inflammatory response and then disappear; or remain there. It may sometimes have a progressive quality, not unlike what happens in some forms of multiple sclerosis, where the brain disease appears to progress independent of the peripheral immune system.

What do basic scientists take from meetings like the Nikolas Symposia?

Clinical scientists are a dying breed because today clinicians have less and less time to undertake basic research on top of their clinical duties. When basic researchers meet clinicians and some of their patients, they learn about the real disease, the variable ways in which the disease presents, the problems of diagnosis. Textbooks all too often give a highly stereotyped version.

Could other disease areas benefit from similar meetings?

Some children with neuroblastoma develop Dancing Eye Syndrome (DES: opsoclonus myoclonus). The neuroblastoma evokes an immune response, which attacks the tumour, but apparently also the brain: in particular the cerebellum and centres controlling eye movements, leading to ataxia and the uncontrollable eye movements. A similar meeting now exists to bring together the families of children with DES, clinicians who treat the children, and basic scientists. Again these meetings were established by parents of affected children. There is usually a lack of awareness of rare diseases and it is important for patients and carers to know that others share their problem and such meetings give scientists and clinicians the impetus to study rare diseases.

Is there any resistance to small meetings?

I think not. Speakers at both the Nikolas Symposia, and the DES meetings, give their talks but much time is devoted to open and frank discussion. The discussion is fundamental. At the usual conference halls with hundreds of attendees there is little critical discussion: there is a kind of censorship in science now. It takes a few committed people to set something like this up and, in the end, to make a difference to the children.