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UK launches stem cell bank

The UK has officially opened a Stem Cell Bank, the first of its kind in the world. Two human embryonic stem cell lines were deposited in the Bank on the day it opened (19th May 2004).

The cell lines were developed separately by researchers at King's College London, and the Centre for Life in Newcastle-upon-Tyne, UK. Eventually, the Bank will hold stem cell lines derived originally from embryonic, foetal and adult tissues.

The Bank is hosted by the UK National Institute for Biological Standards and Control (NIBSC) and funded by the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC). Its responsibility is to store, characterise and supply ethically approved, quality controlled stem cell lines for research and ultimately for treatment.

"RESEARCHERS CAN EXPLORE ITS ENORMOUS POTENTIAL"

Professor Colin Blakemore, Chief Executive of the MRC said, 'Stem cell research offers real promise for the treatment of currently incurable diseases. The Bank will ensure that researchers can explore the enormous potential of this exciting science for the future benefit of patients'.

Professor Julia Goodfellow, Chief Executive of the BBSRC, said, 'Stem cell therapy will remain a dream unless we can understand and control the processes that switch these cells into specialised types such as brain or pancreas cells. The Bank will help us to achieve this by providing isolated and well-characterised cells for research'.

In a further boost, the following week, the MRC announced 57 grants totalling £16.5 million for stem cell research in universities across the UK.

*Meanwhile US universities are circumventing US government regulations. Institutions receiving federal funding are allowed to carry out stem cell research only on 60 established stem cell lines. Harvard is the latest university to establish an institute that uses private funding for the research (*BMJ* 2004; **328**, 1094), and which therefore will be allowed to continue with stem cell research.

The Harvard institute involves 14 of its school and hospitals and nearly 100 researchers and scientists. The University aims to raise $100 million (€84 million) for the institute. Stanford University, the University of Wisconsin and the University of Minnesota, are among the others with plans to set up privately funded stem cell research centres.

Art in oncology competition

Entries are now being accepted for an international art competition, *Oncology on Canvas: Expressions of a Woman's Cancer Journey.* Women who have survived breast and ovarian cancer, their oncologists, nurses, families and friends are invited to submit artwork that represents their experiences with cancer.

'Entries should portray a woman's cancer journey in ways that inspire others to follow,' says sponsor Lilly Oncology. Media accepted include oils, watercolours, acrylics, photographs, pastels and charcoal.

The closing date is 29th October, 2004 and winners will be notified in November 2004. A public viewing of the exhibition will take place on 3rd December 2004 at the Royal College of Art in London.

For further information, contact Jeremy Parsons, Art Exhibition Director at j_parsons@dial.pipex.com

Aspirin 'a chemopreventive agent'

Prospective clinical trials are now needed to establish the value of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) as chemopreventive agents for breast cancer, say US researchers. They found further evidence that regular use of NSAIDs may be effective, especially in postmenopausal women (*JAMA* 2004; **291**, 2433–40).

The population-based case-control study of women with breast cancer included 1442 cases and 1420 controls. In-person interviews were conducted on Long Island, New York, between 1996 and 1997.

Overall, an inverse association was found between aspirin use and breast cancer risk. Women who had ever used aspirin had an 0.8 risk of breast cancer, compared to non-users. This inverse association was strongest among frequent users, and among those with hormone receptor-positive cancers. It was evident for every subgroup except ER, PR-.

Frequent use of aspirin might be predicted to reduce COX-derived prostaglandins, thereby suppressing aromatase activity and lowering levels of intramammary oestrogen. The authors say it will be important to determine, for example, whether NSAIDs suppress levels of progesterone in breast tissue.

But they speculate, 'Our results raise the possibility that combining an NSAID with an aromatase inhibitor might permit lower doses of aromatase inhibitor to be used [in chemoprevention] without a loss of efficacy'.

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Thinking inside the box

To ban or not to ban, that is the question – or is it? Because many people believe the disadvantages vastly outweigh the advantages, direct-to-consumer advertising (DTCA) is legal in only two countries – the USA and New Zealand. However, New Zealand is now thinking of reintroducing a ban. But, although banning DTCA is one option, researchers at Dartmouth Medical School, NH, USA, have come up with another idea – the inclusion of a prescription drug-benefits panel in all advertising material. The box is modelled on the US Food and Drug Administration's (FDAs) nutrition facts box, which is required on food packaging. The information would use data from clinical trials to emphasise exactly how effective the drug is compared with placebo.

DTCA's main advantage is that it informs consumers about the products available. This is especially important in countries such as New Zealand, where many drugs are not subsidised by the state, says Leslie Clarke, Researched Medicines Industry, New Zealand. DTCA can also help to ''get consumers who have underdiagnosed medical conditions to talk to their health-care professional'', comments Thomas Abrams, Director of the FDAs Division of Drug Marketing, Advertising, and Communications, and ''that would be positive for public health'', he adds.

In a survey of 1300 US physicians, Joel Weissman and colleagues from Massachusetts General Hospital, MA, USA, found that of the 643 responders, more than 70% thought that DTCA helped to educate patients, and 67% thought that it helped them to have better discussions with patients *(Health Affairs*, published online April 28, 2004; DOI: 10.01377/ hlthaff.W4.219).

However, the researchers also found that 80% of doctors did not think that the health information presented to consumers was balanced, and could lead patients to seek unnecessary treatment. Thus, DTCA increases the burden on the health-care system by leading to more physician visits, putting pressure on physicians

"80% DOCTORS BELIEVE ADVERTISING PROMOTES UNNECESSARY TREATMENT"

to prescribe drugs that patients have seen advertised, and promoting overuse of costly drugs. Because the information provided in DTCA is usually written qualitatively, and with the intention of selling the drug, the overall message can be misleading, with many patients wrongly assuming that the drug always works, or works extremely well.

At present, DTCA is tightly regulated in both the USA and New Zealand. But although the regulations require disclosure of common and serious adverse events, together with the approved indication, contraindications, and appropriate precautions for use, they do little to increase the accuracy of the benefit claims.

But is a complete ban necessary? When Europe revised their stance on direct-to-consumer advertising in late 2003, they decided to uphold the ban. Margaret Ewen, Health Action International, Amsterdam, Netherlands, comments, ''people need quality, reliable, independent, and comparative information about all treatment options (pharmacological and non-pharmacological), including the option not to treat. The purpose of advertising is to sell the product. Clearly, it isn't what Europeans want''. Yet the situation is quite different in New Zealand: independent research (as yet unpublished) done by investigators at Massey University, New Zealand, on New Zealanders' attitudes to DTCA found that only 20% of the public favour a complete ban. Of those in favour of retaining DTCA, a substantial number expressed a preference for a clearer presentation of risk and benefit information, according to Clarke.

To address the issues inherent in misleading wording, Steven Woloshin and colleagues from Dartmouth Medical School, NH, USA, interviewed more than 200 members of the general public to measure their reaction to a box that contained the benefits of the drug compared with placebo. Their findings (*Health Affairs*, published online April 28, 2004; DOI: 10.1377/ hlthaff.W4.234) showed that people could correctly extract and understand the implications of the data in the benefit box, and their perceptions of drug benefit decreased by 37% after seeing advertisements that contained the box, compared with conventional advertisements.

Inclusion of such a box in DTCA ''moves the debate further in focusing on how to make the advertisements

"EXTRA INFORMATION DECREASED PUBLIC PERCEPTION OF BENEFIT"

function better'', says Steven Woloshin. Robert Ehrlich, DTC Perspectives, NJ, USA, thinks that ''the box proposal makes a lot of sense. It is designed to focus consumers on key health risks rather than the litany of risks now in most advertisements''.

The researchers presented their results at an FDA public meeting on DTCA in September, 2003. Since then, in January, 2004, the FDA issued a draft guidance in which they proposed the use of section called *Highlights of Prescribing Information*, which would use language easily understood by the average audience, ''the information that is most important to safe and effective use''. However, the new guidance does not specifically mention provision of drug-benefit data, which Woloshin and colleagues found ''disappointing''.

In countries where DTCA is legal, the best approach is to make the information as balanced and accurate as possible, and this information can then be used to improve the relationship between patient and doctor. ''If a patient brought the advertisement in to the doctor, the ready access to efficacy data would help inform their decision. It is not usually easy (or feasible) to obtain this kind of data during an office visit'', concludes Woloshin.

Anna York

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EUROFILE

Disharmony in Clinical Trials Legislation

Member States have made widely differing interpretations of the European Clinical Trials Directive. The result, as campaigners feared, is a patchwork of different legislative frameworks across Europe. This, they say, will increase the costs of clinical trials, ultimately reducing the numbers of trials taking place.

The Directive, adopted in May, 2001, was intended to ensure a high level of protection for patients taking part in clinical trials, while also streamlining legal and administrative requirements. Member States were obliged to enforce the Directive by 1st May 2004. Any lingering hopes that national bodies would produce compatible legislation have now been wholeheartedly dashed.

The special position of academic research was acknowledged in the statement, 'Non commercial clinical trials conducted without the participation of the pharmaceutical industry may be of great benefit to the patients concerned', but the Directive did not make provisions for its particular needs. Key problems include the requirement for a single sponsor to take overall financial and legal responsibility for a trial. In academic research, typically conducted by a network of centres, a single centre would struggle to shoulder this burden. Further, the Directive requires the sponsor to provide the investigational product free of charge, even if the same drug would be routinely used to treat patients outside of trials. Detailed dossiers of any products involved must be supplied, even if, like aspirin, the drugs have been widely available for decades. Part of this information is frequently unavailable to academic researchers.

These issues have been highlighted for months now, in particular by EORTC and FECS. Some Member States have strived to address them in their national legislature but calls for States to adopt a unified approach appear to have been largely ignored. The result is that there are almost as many different legal frameworks as there are Member States. One of the central aims of the Directive, to harmonise requirements across the continent, has not materialised.

In Belgium, for example, the EORTC has worked closely with Belgian authorities and negotiated almost an opt-out from the Directive for academic research. Academic research is exempt from paying some of the fees which would have been required for having a new trial assessed by regulatory authorities and ethics committees. The sponsor will not have to pay for drugs which are already on the market if they are being used for a recognised indication, nor will it have to provide detailed dossiers for established drugs.

Sponsors of pan-European trials run from outside of Belgium will require recognition by the Belgian King before they can benefit from these exemptions for academic research. This is an extra hurdle for sponsors, but Dr. Patrick Therasse, Director of the EORTC Data Center, said that this will only pose a problem for small research networks without adequate infrastructure. 'This has never been written down as an intention, but will be a result of the Directive'.

In Germany, where the legislation is not yet completed, Dr. Therasse was optimistic that a similar special arrangement for academic research could be included.

The UK has a higher proportion of academic research (as opposed to that sponsored by the pharmaceutical industry) than many other countries and could have been particularly hard hit by the Directive. After consultations by the Department of Health with Cancer Research UK and the Medical Research Council, the new UK regulations incorporate a broad definition of sponsor, which allows the responsibilities of the sponsor to be split between participating centres.

Professor Alex Markham, Chief Executive of Cancer Research UK, said this was a pragmatic way of implementing the Directive. 'The Department of Health has worked hard to reach a point where publicly funded clinical trials can continue under the new regulations'.

France has said that its existing legislation adequately meets the Directive's requirements and has no plans to introduce further measures. Swedish regulations were in place ahead of the deadline and are widely seen as helpful for academic research. Italian regulations were also agreed early and are causing difficulties for researchers, but these are not insurmountable, according to Dr. Therasse. 'Those setting up clinical trials are facing increased administration, but as long as they meet the extra requirements, the trials are going through the new system. The problem is most acute for smaller centres which are not accredited. Larger centres have the infrastructure – which costs money because it is extra work – but they can meet the new requirements,' he said.

"PUBLICLY FUNDED TRIALS CAN CONTINUE"

Legislation in the Netherlands has been delayed until July 2004. Professor Jaap Verweij (Erasmus University Medical Center, Rotterdam) said that while he is optimistic that many problems associated with the Directive will be solved, he expects the increased bureaucracy to cause problems. 'I have been personally involved in preparing proposals. It will cost between €15 and €20,000, before any patient is entered in a trial, before even the ethics committee has looked at it. That is money spent for no return,' he said.

"DISPROPORTIONATE BUREAUCRACY COMPLETELY FAILS PATIENTS"

Dr. Richard Sullivan, Head of Clinical Programmes at Cancer Research UK, also criticised the quality

(continued overleaf)

Gene signature predicts recurrence in Dukes' B

'High-risk' Dukes' B colon patients can be selected using a 23-gene expression pattern, say US researchers (*JCO* 2004, **22**, 1564–71), who used it to identify patients at 13-fold risk. ''Adjuvant chemotherapy in resected colon cancer may be guided in the future by this prognostic marker'', they said.

Surgical resection for patients with uninvolved lymph nodes (Dukes' A and B) is highly effective for localised cancers, but a substantial proportion – approximately 25–30% – of Dukes' B patients have recurrences. The prognosis for these patients is poor. A postoperative course of chemotherapy is now the standard of care for Dukes' C patients, but it is unclear whether Dukes' B patients have a survival benefit following such chemotherapy, and this has to be weighed against the side-effects of treatment. A recent meta-analysis showed no benefit for chemotherapy in this group. Selection of 'high-risk' Dukes' B patients is essential and several promising markers have been proposed, but none has been widely adopted.

The US group, led by Dr. Yixin Wang (Veridex, San Diego, California, US) believes the genetic signature may be the answer. Colon cancer progression is a function of multiple genetic events. They used micro-array gene expression analysis and classification methods in two predictive approaches using archived primary tumour material. Samples were collected from 74 patients at the time of surgery. The first approach was not predictive.

The second – using a clustering analysis – successfully identified a 23-gene predictor of patient outcome. In a validation test, it had an accuracy of 72% (28 of 36 patients), a sensitivity of 72% (13 of 18 patients) and a specificity of 83% (15 of 18 patients). The 23-gene signature was able to predict patients with a 13-fold (Odds Ratio) higher risk of developing tumour relapse within 3 years. Several of the genes identified were involved in cell proliferation, tumour progression and immune processes.

The Odds Ratio was much higher than that for lymph node status, a characterised prognostic factor in colon cancer. The researchers said the study ''strongly indicated'' that colon cancer prognosis can be derived from the gene expression profile of the primary tumour.

Identification of such genes will provide targets for therapeutics and increase our understanding of colon cancer biology. It will also impact upon current clinical practice. ''This prognostic signature will provide a powerful tool to select patients who are at 'high-risk' and ensure that they receive adjuvant treatment'', they concluded.

An accompanying commentary (*JCO* 2004, **22**, 1538–39) noted, ''This is the first example in colorectal cancer of a genomics approach systematically identifying molecular markers for colon cancer prognosis…it points towards the redefinition of the staging of colorectal cancer based on a genetic signature rather than solely on the anatomic and pathologic staging of the primary tumour''. However, Dr. Patrick G. Johnston (Queen's University, Belfast, N. Ireland) is more cautious about its potential to determine treatment strategies. ''A poor clinical prognosis does not necessarily indicate a benefit from an intervention,'' he wrote.

Emma Cannell

Clinical Trials Disharmony

(continued from previous page)

of the Directive. 'Its disproportionate bureaucracy completely fails patients. We have always treated all clinical trials in the same way but this legislation covers drugs only, not surgery or radiotherapy. It is not going to increase the protection of patients. And it will not lead to harmonisation across Europe, which was one of the main aims'.

Increased regulations increase cost, said Dr. Sullivan. 'Over the next year or 18 months, we, along with the National Cancer Research Institute, the National Cancer Research Network and the Medical Research Council, will be assessing the costs of trials. We are expecting the Government to support any increases in the costs of trials and they have given us assurances that they will do so'.

Another unanticipated problem is the new reluctance of pharmaceutical companies to provide free drugs for patients in whom everything else has failed. Previously, companies were often willing to provide drugs to prescribers for compassionate use in patients for whom all other approaches had failed. Now, however, if the drug has not been registered for the intended use, this would be considered a clinical trial. Companies are therefore less willing to shoulder the responsibility (aside from in specific trials). Companies may also become reluctant to provide investigational drugs for investigator-sponsored trials because of the risks inherent in taking on the sponsor's responsibilities under the new legislation.

Campaigners agree that it will take time and experience under the new Directive to properly assess its impact. EORTC is monitoring the impact of the Directive on all EORTC trials activated within the first 6 months. A report is due in November, 2004. Ms Kathleen Vandendael, Executive Director of FECS, said she will gather, with the help of EORTC and other member societies, information about how the Directive has been implemented in various Member States. On the basis of this information, she will produce an overview for the European Commission. FECS together with the European Commission is intending to arrange a meeting before the end of the year, bringing together all interested parties – national and European competent authorities, academic researchers, and so on – to discuss the overview. 'We want to pinpoint aspects which are absolutely unhelpful, and provisions which are useful, so that Member States could consider amending their own laws accordingly,' she said.

Helen Saul

PODIUM

The Financial Foundations of EORTC

Sir Christopher Mallaby is Chairman of the EORTC Foundation. He worked for the British Diplomatic Service for many years, and was, in turn, Deputy Secretary of the Cabinet, Ambassador to Germany and to France. Sir Christopher is a Managing Director of UBS Investment Bank and a director of several other companies. His voluntary roles – besides that at the EORTC Foundation – include the Chairmanship of Somerset House Trust and 3 university positions.

Sir Christopher Mallaby

What does the EORTC Foundation do?

We have provided the core funding for EORTC for the last 25 years. This ensures that EORTC remains independent and is not dependent on the private sector to cover its costs. We also fund scholarships and individual research projects.

How does the Foundation raise its money?

We receive money from the national cancer leagues and national charities such as Cancer Research UK, whose research benefits from the services provided by EORTC. This money – about €1 million a year – is channelled through the Foundation and on to EORTC, and this goes towards EORTC's core funding. We also organise fund-raising events such as the gala dinner at the EORTC-NCI-AACR Congress in Geneva, Switzerland, in September 2004. The Mariinsky Opera from St Petersburg will be performing, there'll be a talk on cancer research and the event will raise several €100,000s for the Foundation. We also receive occasional but significant grants from other foundations or from individuals. This money, again, goes through us, to EORTC.

How heavily does EORTC rely on the Foundation?

Over the past 7 or 8 years, we have tripled the amount we provide. But over the same period, it has gone down as a proportion of the money EORTC needs from one-third to a tenth as EORTC has expanded its activities and regulatory costs have increased.

What constraints are there on your activities?

We would not want to undertake fundraising programmes which clash with the efforts of the cancer leagues who fund us. So we wouldn't go into retail fundraising, asking millions of individuals for donations. When we organise a gala, we take advice from the national cancer league to make sure the timing of the event will not undermine anything they are running. We have managed, to an extent, to find individual sources of money. But as the costs of trials increase following the EU Clinical Trials Directive we are thinking more about new sources. We need to add considerably to our contribution.

How will you increase the contribution?

We are looking for methods of fundraising and sources of money which will not cut across the fundraising activities of the national leagues. That's the conundrum we have to solve. There are multinational companies which do not belong in any particular European country, and which have their headquarters in the US or Japan, for example. This is the kind of idea we are investigating.

The EORTC provides services of extraordinarily high quality and when the costs of these services go up, as they will, we need to provide more money. National leagues and charities who benefit from EORTCs work may be asked to increase their contributions but we also want to find other approaches which will help to maintain EORTCs research and trials.

It has been predicted that the costs of trials could increase three fold. How will this affect the Foundation?

It won't alter the nature of the Foundation's role, but will be a step-change in terms of the amount of money needed. We will continue with our current activities with the leagues and the gala dinners but we are looking for new sources as well.

What is the time frame for this?

It takes time to bring new sources on stream, but we are looking to make a difference starting this year. When EORTCs current problems became clearly visible in September 2003, we made an immediate response and increased the money we provide by €100,000 this year. Now, our target is to make a big effort to make a permanent increase in the money we provide.

Were you involved in any lobbying about the EU Clinical Trials Directive?

As it happens, the EORTC and others have done their own negotiation but I have always said I am willing to help in any way I can. I have done similar work for another medical charity.

What is your role at EORTC Foundation?

As the Chairman, I work alongside our executive, Mrs Victoria Agnew and a Board of distinguished people, giving advice, helping with events, making sure that the Foundation works and we get results. It's a hands-on role, everything from negotiating with EORTC itself about its financial needs to finding new sources of income or sponsors for events, persuading volunteers to help or selling tables for the gala dinners.

Why do you do it?

I have connections and experience through my diplomatic career, and now as a banker, within the business world. It's a privilege to have the opportunity to take on this useful role in the great cause of cancer research.