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Molecular Targets and Cancer Therapeutics

The 14th EORTC–NCL–AACR Symposium on Molecular Targets and Cancer Therapeutics, held in Frankfurt, Germany (19–22 November, 2002) was attended by 2000 delegates from around the world. More than 560 abstracts were presented; the following are highlights from the press conference

Lung cancer: First clinically useful marker

Increased expression of a DNA repair gene may be the first clinically useful independent prognostic marker in non-small cell lung cancer (NSCLC), US researchers say. A team led by Dr Gerold Bepler and Dr George Simon at the H. Lee Moffitt Cancer Center, Florida, found a correlation between levels of ERCC1 expression and survival. The finding may help select patients most likely to benefit from adjuvant chemotherapy, they say

The US team tested tissue from 49 patients with NSCLC ranging from stages 1A to IIIB for ERCC1 expression. All patients had undergone surgery. Patients with low levels of ERCC1 had a median survival of 35 months, those with medium levels, of 62 months, and those with high levels, of 94 months.

ERCC1 is a DNA nucleotide excision repair gene which corrects the mistakes sometimes made when cells divide and protects against cancer. However, ERCC1 also repairs damage in treated cancer cells. Platinum-based chemotherapy such as cisplatin bonds the DNA double helix in the cancer cell so that, instead of unwinding to start the process of cell division, the strands break. ERCC1 mends the damage in the cancer cell and makes the tumour drug-resistant.

Dr Bepler said that although the results were initially unexpected, they make sense. 'Once the bulk of a cancer is removed by surgery, patients with high levels of ERCC1 are better off, whether or not they have had adjuvant treatment, because their more effective repair gene will swing into action against these stray secondary cells. Because it is so early in the cancer process it will have a good chance of repairing the damage and stopping the relapse of the cancer before the cells run out of control. If ERCC1 levels are low, there is less chance the rogue cells will be repaired.

'ERCC1 is truly a double-edged sword. In early cancers or cancers where the bulk of the tumour has been removed, high ERCC1 is good. In advanced cancers it's bad because it keeps repairing the damage done by cisplatin or carboplatin so the patients respond poorly to chemotherapy,' he said.

Patients with low ERCC1 have a poorer prognosis but are less likely to be drug resistant and may therefore be more likely to benefit from chemotherapy. Dr Bepler said the results will need to be validated in future clinical trials: 'There is still a lot more to be done to evaluate our findings, but this is the first independent marker for NSCLC with potential clinical utility.'

Chemoprevention trial in oral cancer

Norwegian researchers are planning a phase III randomised trial to investigate whether COX-2 inhibitors may prevent oral cancer. Researchers at the Norwegian Radium Hospital and the University of Oslo have demonstrated that COX-2 is up-regulated in high-risk oral lesions.

The study presented at the symposium included 30 patients with healthy oral mucous membranes, 22 with dysplastic lesions and 29 with oral cancer. They measured COX-2 expression and DNA aneuploidy.

All the healthy group had normal DNA and only one had COX-2 expression. Among those with cancer, 88% had COX-2 expression and 94% had aneuploidy. Importantly, among those with dysplastic lesions, COX-2 was only expressed in the 9 patients who also had aberrant DNA. Of these 9 patients, 7 were followed for 5 years and 6 went on to develop oral cancer.

Lead researcher Dr Jon Sudbø said oral cancer is ideal for investigating chemoprevention because it is normally preceded by readily detectable lesions. There is typically a lead-in time of 5–10 years between the occurrence of dysplasia and the development of cancer.

The chemoprevention trial will include 350 patients with aneuploid white patches in their oral mucosa, randomised to receive celecoxib for 5 years.

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BRCA2's workings uncovered

Insights into the structure of the complex formed by the BRCA2 protein and a DNA repair enzyme, RAD51, have been reported by UK scientists (*Nature* 2002 **420**: 6913, 287–293). They say the discovery has 'exciting implications' for drug development.

The group, led by Professor Ashok Venkitaraman (University of Cambridge, UK), established the structure of a complex between an evolutionarily conserved sequence in BRCA2, the BRC repeat, and a domain of RAD51. The BRC repeat mimics a motif in RAD51 that serves as an interface for oligomerization between individual RAD51 polymers. In this way, BRCA2 controls the assembly of the RAD51 nucleoprotein filament, which is essential for strand-pairing reactions in DNA recombination. Mutations affecting the BRC repeat disrupt the reaction with RAD51, and allow cells to develop potentially cancerous mutations.

Professor Venkitaraman said, 'When the BRCA2 gene is faulty, a cell's genetic information becomes increasingly unstable, making it more likely that cancer will develop.'

The work showed that the RAD51–BRCA2 interaction 'will be particularly vulnerable to small-molecule inhibitors.' The authors concluded, 'Because BRCA2 and RAD51 participate in the repair of DNA breakage during DNA replication, such inhibitors may prove useful adjuncts to radiation therapy or anti-cancer drugs that induce DNA damage or interfere with replication.'

The researchers are funding by Cancer Research UK, the UK's Medical Research Council and the Wellcome Trust. Sir Paul Nurse, Chief Executive of Cancer Research UK described the study as 'an exciting leap forward in our understanding of the disease on a molecular level'.

Pre-operative scanning

Pre-operative staging with MR mammography (MRM) and positron emission tomography (PET) can influence surgical treatment in up to 15% of women with breast cancer, German researchers say. They conclude that it is 'clinically justified' to include staging by one of these methods in patients' pre-operative work-up (*British Journal of Radiology*, 2002, **75**, 789–798).

The researchers, from the University of Ulm, studied 43 patients with histologically confirmed breast cancer. They compared the efficacy of clinical data and conventional diagnostic techniques alone; or when combined with these scanning methods. They considered the diagnosis of primary tumour, contralateral carcinomas, bifocal, trifocal or multifocal disease, as well as non-invasive cancer portions and tumour size.

Surgical planning was optimised in 6 patients, or 15% of the total. Contralateral carcinomas that had escaped conventional diagnostic techniques were uncovered; more reliable size determination in one patient meant a more generous resection was undertaken, possibly removing the need for a secondary resection. Other patients had radical surgery, rather than the originally planned breast conservation.

MRM was slightly superior to PET, but not significantly so. The authors acknowledge that these methods are more costly than conventional staging techniques but say, 'Larger studies must address the question of whether this enhanced diagnostic accuracy can be justified financially, taking into consideration the fact that secondary costs may actually be reduced by the resulting optimised therapeutic management.'

Lumbar puncture in children with ALL

Attempts should be made to reduce the risk of traumatic and bloody lumbar puncture, say American researchers. They say some risk factors can be modified in children with ALL (*JAMA* 2002, **288**, 2001–2007).

They examined risk factors in 5609 lumbar punctures on children with ALL. Some were unmodifiable: black race, age less than 1 year, a traumatic or bloody previous lumbar puncture in the past 2 weeks and a previous lumbar puncture performed when the platelet count was low.

However, they noted that procedural changes in the hospital (St Jude Children's Research Hospital, Memphis, Tennessee) caused an abrupt reduction in bloody and traumatic LPs. Previously LPs were performed in inpatient wards or outpatient clinics with no or only conscious sedation. After May 1995, LPs were performed in a dedicated area, with dedicated staff and general anaesthesia. There was no difference in the level of training of the oncologists, other doctors and nurse practitioners who performed the procedure. The researchers say 'We attribute the effect to these changes'.

Low platelet count was another strong risk factor and the researchers say, 'In those settings in which traumatic LP is particularly undesirable and the benefit of transfusion outweighs the disadvantages, such as the diagnostic LP in a child with ALL and circulating leukaemic cells, platelet transfusion for a count of $100 \times 10^3/\mu L$ or lower is warranted.'

The strongest predictor was a short interval since the previous procedure, and the authors advise that in patients with definite evidence of leukaemia, 'We now administer intrathecal chemotherapy immediately after obtaining CSF for examination with the diagnostic LP, obviating the need for repeated LP for intrathecal chemotherapy in a short period.'

Blood in the CSF alters the cell count, increases the protein level and can cause false-positive culture and cytologic results, with consequent diagnostic confusion. Bacteria or leukaemic cells introduced into the CSF as a result of traumatic LP can worsen the patient's prognosis. In this study, 10% of LPs were bloody, and the researchers say that attempts should be made to reduce the risk. They say that their findings 'translate directly into recommendations for patient care.'

EUROFILE

EU countries 'must harmonise clinical trial regulations'

Red tape and disparate legal regulations may hold back international clinical trials in Europe, according to Françoise Meunier, Director-General of the EORTC. A lack of harmonisation in national legal obligations will jeopardise progress in establishing state of the art treatment strategies, she said: 'It leads to pitfalls without improving patients' safety or the quality of science and cancer care.'

'KEY AREAS OF RESEARCH COULD BE MARGINALIZED'

The EU Directive on Good Clinical Practice was adopted in 2001 and is due to be implemented in member states' law by May 2003 and applied by May 2004. It is a step forward, but there is still a risk that it will fail to establish the appropriate legal and regulatory framework to avoid duplication of research and waste of resources. She said that for it to succeed, its implementation into national laws must take pan-European research into account including more effective evaluation of innovative compounds, but also independent academic trials not aiming at drug registration.

Key topics in the Directive are open to too broad an interpretation by national authorities, she said. These include ethical approval and protocol amendment procedures, regulations for reporting serious adverse events, informed consent documentation, requirements for drug labelling, costs of non-sponsored trials, translational research issues such as exchange of tumour materials and tissue research and insurance requirements by ethics committees.

She acknowledged that the original goal of the Directive was to facilitate clinical research and promote patient participation in Europe, but said that regulatory hurdles will probably increase. 'It remains to be seen whether the implemention of the Directive will actually decrease the high level of complexity faced by investigators and promoters of research' she said.

'There is a real risk that European health policy makers and national authorities may marginalize key areas of biomedical and health research by developing policies without fully taking into account the scientific environment and economic structure of independent research.

'The creation and strengthening of networks of excellence within the European Research Area will be seriously jeopardised unless there are appropriate strategies to initiate and effectively conduct pan-European clinical trials and tissue research under an optimal legal framework that can collaborate with countries such as the USA, Australia and Japan as equal partners,' she concluded.

'THE COST OF CLINICAL TRIALS COULD INCREASE BY 30%'

Professor Meunier's comments follow a Forum in Brussels (European Forum on Good Clinical Practice EFGCP, 6th September, 2001, and followed up on December 2nd, 2002). Delegates attended from 8 Member States, Switzerland, the USA, Turkey, Central and Eastern Europe. A position paper from the meeting stated that implementing texts on the Directive represent 'a considerable contribution to good clinical practice'. They fill the regulatory deficit which the EU has had for many years compared to the USA 'and thus adds credibility to the outstanding clinical work produced in general in the EU.'

The position paper highlighted 'excessive' requirements, which it said could reduce the number of clinical trials placed in the EU. For example, the documentation required to start a trial in the EU 'will be the most voluminous in the world,' partly because redundant information is required. Other problems include:

- The proposed system does not sufficiently protect the sponsor's intellectual property
- Regulatory approval of protocol amendments is necessary in every member state, with no guarantee that amendments will be approved or rejected in each, in order to maintain protocol consistency
- More work is imposed on investigators and ethics committees
- Authorities and ethics committees are not given time limits for amendments, which threatens trial timelines
- There is no provision for an EU-wide list of disqualified investigators
- Inconsistencies with international texts have crept in. In relation to ICH-GCP and it would be detrimental not to pursue the initial attempt to harmonise US, Japan and Europe.

The position paper concluded that costs of clinical trials could increase by 30%. Further, sponsors will be forced to greater pan-European centralisation of their clinical research departments, possibly at headquarters which are often outside the EU. The risk of non-compliance is particularly preoccupying for clinical trials driven by small pharmaceutical sponsors, start-up companies, academia, non-governmental organizations, and the public sector itself, because these sponsors do not have the project management systems in place to feed the system with this amount of information on a continuous basis.

An overwhelming majority of participants at the Forum felt that the guidance will not make the EU a better place for placing clinical trials.

Helen Saul

Theoretical Impact of an HPV vaccine

An HPV vaccine would greatly reduce the need for colposcopy, biopsy and treatment of cervical cancer, but screening programmes would probably still be necessary, say US biostatisticians (*Epidemiology* 2002, **13**, 631–639). Their conclusions are derived from mathematical models which explore the population-level impact of an HPV vaccine.

They found that under a specific set of assumptions (including 90% coverage, vaccine 75% effective a mean 10-year immunity), vaccinating both men and women leads to a 44% decrease in the endemic prevalence in women of the HPV types the vaccine is directed at. Vaccinating only women leads to a 30% decrease in HPV prevalence. 'Over a broad range of assumptions, a female-only vaccination strategy would likely be 60%–70% as efficient as a strategy that targets both sexes,' they wrote. Targeting high-risk individuals appears less likely to succeed, in part because of the difficulty in identifying them.

Further, a reduction of 60% in the incidence of high-risk HPV infections results in a smaller reduction in the incidence of CIS and ICC, because some lesions avoided through vaccination are replaced by others caused by different high-risk HPV types.

Vaccination should decrease the risk of CIS and ICC but is unlikely to completely eliminate it so 'screening programs must continue in some form,' they write. However, vaccination may still be cost-effective if it eliminates the need for follow-up and treatment of a substantial number of HPV-associated lesions. In addition, it may be possible to reduce the frequency of screening if the vaccination programme is successfully implemented.

The authors say they have had to make simplifying assumptions, for example about patterns of partner change and mixing. Knowledge about the natural history of HPV infection is still incomplete. 'If infected individuals remain sporadically infectious.. over long periods, then a vaccination program that prevents such infections would be even more attractive,' they say.

An accompanying editorial (*Epidemiology* 2002, **13**, 622–4) agrees that models do not have to be perfect to provide insights and to identify new research directions. But it calls for 'communication about models in a fashion that makes it easier to build on the work of others.' Dr James Koopman (University of Michigan, Ann Arbor, USA) said, 'It would help to have software that allowed modelers easily to reproduce a published model analysis and then to explore the robustness of the assumptions of that model.'

New database of digitised mammograms

A database of digital mammograms is being created in the UK by Oxford University, IBM and the UK Government. Working together, they say they aim to build the 'world's largest database of mammograms'.

The project, called eDiamond, started collecting data from Oxford, Edinburgh and London in November 2002. Digital mammograms taken in routine screening programmes will be held locally, but available as part of the growing database, encrypted to ensure confidentiality.

The database will allow radiologists faced with a lesion of unclear pathology to call up similar images from the past. The radiologist will draw round the lesion, ask to see similar images, and be shown other images of similar shape, size and tissue density, which may help in determining clinical management. Dr Ruth English (Oxford University, UK) said, 'It's interesting, but exactly how clinically useful the system will be has to be evaluated.'

More immediately, the project should help in training and research, as trainees with access to a library would be able to undertake some of their training unsupervised. 'The training of radiologists and radiographers takes huge resources. Radiology is an expanding field, with the development of PET, MRI and other new scans, and we are going to need hundreds more than we can train. There is no way that we can keep up with the demand, with current teaching methods. We're hoping that access to a virtual library of mammograms will allow us to take more trainees per year through the training system,' said Dr English.

In research, eDiamond will link up with existing epidemiology projects, such as the Nurse Student Trial in Scotland, which is collecting data on lifestyle. The database should allow researchers to examine questions such as the relevance of breast density or fat content, and how they are affected by lifestyle or geographic factors. Dr English: 'There seems to be some correlation between mammographic appearance and breast cancer risk. If we had a proven relationship, we might be able to target our resources towards those at increased risk. If we knew that women with a particular pattern of breast density are at higher risk, we could maybe screen them more often, and others, less often. This is not a proposal, it's just a potential advantage if the data comes up in favour of it.'

IBM and the UK Government have invested Euro 6 million in the development of eDiamond. It is based on software developed by Mirada Solutions, an offshoot company from Oxford University.

UK Campaign on Lung Cancer

The UK Cancer Charities, Macmillan Cancer Relief and Roy Castle Lung Cancer Foundation, have launched a campaign to increase public awareness of the early signs of lung cancer to encourage people to visit their doctors with concerns. The charities are also calling for 50 more thoracic surgeons, which they say would bring the UK into line with average European standards.

PODIUM

Clinical trials are key to progress

Jens Overgaard is Professor of Experimental Clinical Oncology, University of Aarhus, Denmark. He is a past President of European Society for Therapeutic Radiology and Oncology (ESTRO); a former member of the EU Committee of Cancer Experts and of the board of FECS. He has won numerous national and international awards and is Chair of the Scientific Committee for ECCO -12 (Copenhagen, Denmark, October 2003).

Professor Jens Overgaard

What's your point?
That the key to progress in cancer care is well-conducted clinical trials. Journalists — and everyone else — are dazzled by every new genetic discovery, and of course we need innovation, but until these findings are used on human beings, we will not know whether or not they are useful. We are not treating cancer, we are treating people with cancer, and a whole human being is complex.

Who needs to understand this?
The public need to know that clinical trials are our tools, and that if they participate in clinical trials they will receive excellent treatment.

Governments and health care providers need to understand that clinical trials are an integral part of academic science and we can only advance where they are supported as a standard part of the scenario. All disciplines should participate to advance our common goals. Health care systems want to use treatment approaches shown to be the best, but no one is willing to pay for the development and proof. Setting up trials can be tricky.

Why is that?
I am a radiotherapist and might want to study a new type of radiotherapy called hyperfractionation. Patients receive more treatments than at present, each of reduced dose. In a health care system with waiting lists, it's hard to get support for a new type of treatment which takes longer to carry out. Particularly when you can't claim in advance of the trial that it is any more effective.

An enormous amount of money is going into trials supported by industry. Non-commercial studies are increasingly difficult to perform.

Is the organisation of clinical trials changing?
The traditional model of European collaborative activity, with EORTC at its centre, is ideal for addressing questions and drawing up protocols for the treatment of relatively rare diseases such as sarcoma and certain paediatric diseases. But for common diseases, it does not make sense to involve many institutions, each contributing a couple of patients. So strong regional groups are getting together to create groups of groups. It's a useful structure; it keeps studies local, which makes it easier both to generate support and to implement the eventual results, but it still gives a global answer to the question.

What about the questions we're asking?
Academic groups are asking very simple questions. For example, an EORTC trial which finished last year asked whether women who had undergone breast conserving surgery would benefit from an extra dose of radiation to the spot where the tumour had been. It took more than 500 patients to answer, they came from various countries and the answer was valid, whatever other treatments they had received.

Where is the new biological knowledge taking us?
It is already profoundly important for issues relating to screening, diagnosis, predictive and prognostic factors, and design of new treatment strategies. However, it's an enormous challenge to make this technology useful in daily practice. As it becomes increasingly sophisticated, it is less realistic to imagine that the latest equipment — and the highly trained staff necessary to use it — will be available in every little hospital in Europe. We're going to see more centralised facilities serving a wider area. Information will be collected at the satellite units, sent for interpretation to the centre of excellence and then the diagnosis and/or treatment suggestions will be returned to the satellite unit. This is already happening to some extent in Norway.

In the meantime, how can the lot of European cancer patients be improved?
Through education, especially of the lowest common denominator. It's much better to improve the performance of the worst 25% of doctors than to take the top 10% and make them better. ECCO has always had an important role in education, and it has been upgraded for ECCO-12. There will be educational symposiums, an education book, and a CD ROM containing recordings of talks plus slides.

ECCO is a very special, European conference. It is multidisciplinary, and brings us all together, oncologists, radiotherapists, surgeons, nurses. We should never forget the surgeons, who, even now, are the ones mainly curing cancer. Because of course, the best way of beating cancer is either to avoid it in the first place, or to detect it early and treat it before it spreads.