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## The American Association for Cancer Research held its 100th Annual Meeting in Denver, Colorado (April 18–22, 2009). Robert Day-Webb reports

### Signs of CLL 'years before diagnosis'

People with chronic lymphocytic leukaemia (CLL) exhibit immune system disruptions up to a decade before diagnosis, according to new research (*Proc. AACR 2009 #1680*).

Analysis of 109 blood samples obtained up to a decade prior to diagnosis found evidence of immune disruption in about 40 percent of patients. They had an abnormal free light chain ratio, which is a measure of immune disruption. In one patient, this disruption was noted 9.8 years prior to diagnosis.

This finding provides clues to the aetiology of the disease but also a rationale for future investigations to assess if pre-diagnostic immunodeficiency has an impact on CLL prognosis, the researchers said.

'This is the first prospective study to report abnormal free light chains in people who develop CLL as far as 10 years before,' said Dr. Neil Caporaso (National Cancer Institute, Bethesda, Maryland), co-author of the study. 'However, given that there is no known early intervention that can help with CLL, it is unlikely that the array for free light chains will be immediately useful as a screening tool.'

The research has opened up 'a whole new group of people to study', said Dr. Caporaso.

*R D-W*

### New hope in pancreatic cancer

Targeting stem cells in pancreatic cancer may be a promising way forward, Dr. Rajesh Kumar NV (Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD) told the meeting. He and his colleagues found that a combination therapy of tigatuzumab, a novel humanised death receptor-5 agonist antibody, along with gemcitabine, reduced pancreatic cancer stem cells in mice, and increased time to progression (*Proc. AACR 2009 #1069*).

The finding is consistent with the theory that cancer stem cells are the seeds of the most aggressive forms of therapy-resistant human cancers, he said. 'Emerging studies show that cancer stem cells are indeed more resistant to therapy than other cancer cells and might be the reason why conventional chemotherapy, while reducing tumour size, does not result in long-term cures,' said Dr. Kumar.

The study included mice implanted with human pancreatic tumours, who received either tigatuzumab alone, gemcitabine (the current clinical treatment for pancreatic cancer) alone, or a combination of the two agents.

Researchers found that although treatment with gemcitabine alone reduced tumour size, the remaining tumour cells were rich in pancreatic cancer stem cells and in nearly all cases, the tumours returned.

However, the combined treatment reduced the number of pancreatic cancer stem cells, caused tumour remission and significantly increased the time to cancer progression. 'Targeting cancer-sustaining pancreatic cancer stem cells will be of paramount significance since there are few effective therapies for pancreatic cancer and most of the patients die within the first year of diagnosis,' said Dr. Kumar.

- A second study in pancreatic cancer, conducted by Cancer Research Technology Ltd. (London, UK) and the University of Texas MD Anderson Cancer Center, found promising results with a selective inhibitor of protein kinase D (PKD), called CRT0066101 (*Proc. AACR 2009 #855*).

'We are very optimistic about CRT0066101's pharmaceutical potential. We believe this is the first orally administered small-molecule inhibitor of PKD with significant biological efficacy in pre-clinical animal models of pancreatic cancer,' said lead investigator Dr. Sushovan Guha (University of Texas MD Anderson Cancer Center, Houston, Texas). 'My conviction is that we will show the drug can also prevent the proliferation of cancer cells by blocking their supply of blood – through neoangiogenesis. This would mean it offers a double action treatment but this needs to be proved through further work.'

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## AACR 2009 continued

### Designer T cells in prostate cancer

Early results from a phase I trial suggest that patients' own immune cells may be reprogrammed to attack and kill prostate tumour cells. Researchers used retroviral gene therapy to modify patients' T cells to sensitise them to a molecule that only occurs in prostate cancer – prostate specific membrane antigen (PSMA). The first patients to receive these engineered T cells showed reductions in prostate-specific antigen (PSA) levels of 50–75 percent (*Proc. AACR 2009 #5662*).

T cells are the 'perfect killing machine' when faced with a cell infected with a virus, said author Dr. Richard P. Junghans (Boston University School of Medicine, Providence, Rhode Island). 'We therefore have to fool the T cells into thinking that the tumour has a virus infection.'

A 'haematologic space' was created by chemotherapy to allow the designer T cells to increase in number 100-fold after infusion to increase their potency. Once infused, the modified T cells began to attack cells expressing PSMA – a marker for that activity being the PSA level.

The reduced levels of PSA reported in the first 2 patients treated so far – who both had metastatic disease – were obtained with fairly low doses of the designer T cells of about a billion each. 'With still higher doses of T cells soon to follow in our dose escalation plan, we hope to observe the 100 percent PSA reductions that everyone seeks,' said Dr. Junghans. 'This genetic engineering brings us into a new era of cancer treatment by reprogramming T cells to attack the cancer in the same way that the T cells would normally fight a virus infection. I predict we will see approval of drugs in this category in the next 5 years.'

*Robert Day-Webb*

### Urine test for lung cancer?

Researchers have moved a step closer to developing a simple urine test to identify the smokers at highest risk of developing lung cancer (*Proc. AACR 2009 # 997*). The aim is to spot high-risk people earlier, thereby catching the disease at a preventable or treatable stage, said Dr. Jian-Min Yuan (University of Minnesota, Minneapolis, Minnesota), lead author of the study.

Dr. Yuan also hopes such a test 'might motivate smokers who are having trouble quitting' to finally give up smoking.

The researchers investigated the presence of a known tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), in patients' urine as a predictor of lung cancer risk.

Data was collected from 18,244 men enrolled in the Shanghai Cohort Study and 63,257 men and women from the Singapore Chinese Health Study. Urine and blood samples were collected at enrolment, and stored, and the patients were asked about their smoking habits.

The current study included 246 current smokers who later developed lung cancer and 245 smokers who did not. Patients were divided into 3 groups based on the level of NNAL in their urine.

Compared to those with the lowest levels, patients with a mid-range level of NNAL had a 43 percent increased risk of lung cancer, while those at the highest level had more than double the risk.

Those with the highest levels of both nicotine and NNAL had an 8.5-fold increase in the risk of lung cancer compared with smokers who had the lowest levels. These findings held true even after taking into account the number of cigarettes smoked per day, the number of years of smoking, and other factors.

The next step is to investigate levels of other known tobacco carcinogens in urine, according to Dr. Yuan. 'Smoking leads to lung cancer, but there are about 60 possible carcinogens in tobacco smoke, and the more accurately we can identify the culprit, the better we will become at predicting risk.'

*Robert Day-Webb*

### Molecular profiling in advanced cancer

A personalised approach could help patients with metastatic cancer who have failed to benefit from standard therapy, a pilot study suggests (*Proc. AACR 2009 Late Breaking Abstract #259*).

The prospective study included 66 patients with a variety of advanced cancers who had failed to respond to previous therapies. Molecular profiling of patients' tumours using immunohistochemistry and microarray profiling was used to detect untreated targets. Patients were then placed on appropriate new treatment regimens, and progression-free survival before and after profiling was compared.

After treatment was adjusted, 27 percent of patients (18/66) showed improved progression-free survival. Overall survival in these 18 patients was 9.7 months, compared to 5 months in the rest of the group.

'With this trial, we are showing the power of personalised medicine using the tools we already have available to us. As these tools become more precise and more effective, the value of personalised medicine will increase,' said senior investigator Dr. Daniel Von Hoff (TGen Clinical Research Service, Scottsdale Healthcare, Scottsdale, Arizona).

### Walnuts 'may fight breast cancer'

Eating a couple of handfuls of walnuts a day could prevent breast cancer, research in mice suggests (*Proc. AACR 2009 Late Breaking Abstract #247*).

Half the mice in the study consumed a diet containing the human equivalent of two ounces of walnuts per day; the others were fed a walnut-free diet. Walnut consumption decreased breast tumour incidence by a half, and in mice that did go on to develop breast tumours, the growth rate was slowed by 50 percent. The time to the appearance of the first tumour was 3 weeks slower for the walnut-fed mice which, researchers said, equates to a 9-year delay in humans.

## AACR 2009 continued

### Gene mutations impair response to therapies in mCRC

*BRAF*, *PIK3CA* and *KRAS* mutations, along with loss of *PTEN* expression, impair response to cetuximab and panitumumab in patients with metastatic colorectal cancer (mCRC), according to Italian researchers (*Proc. AACR 2009 Late Breaking Abstract #93*).

Previous studies have shown that the *KRAS* gene is a major predictive biomarker of resistance to epidermal growth factor receptor-targeted therapies, but *KRAS* mutations only account for about 40–50 percent of non-responsive cases. Recent reports, however, have indicated that *BRAF* mutations and deregulation of the *PIK3CA/PTEN* pathway could also drive resistance to anti-EGFR therapy (*see EJC News 2009;45:1 4*).

'This study evaluates, for the first time, the relative contribution of all these molecular alterations. We performed a comprehensive analysis of *KRAS*, *BRAF*, *PIK3CA* gene mutations and loss of *PTEN* expression in patients with metastatic colorectal cancer treated with cetuximab and panitumumab,' said lead author Dr. Federica Di Nicolantonio (University of Turin Medical School, Turin, Italy).

The researchers analysed these four biomarkers, retrospectively reviewing gene mutations in tumour samples of 132 patients with metastatic colorectal cancer who were being treated with cetuximab or panitumumab.

A significant proportion of patients (23/55) with no molecular alterations received some clinical benefit from the treatment, compared to 5 percent (3/56) among patients with one alteration and 0 percent (0/24) for patients with at least two alterations. None of the responders displayed *PIK3CA* or *BRAF* mutations.

'If you consider alterations in all 4 genes, then more than 70 percent of colorectal cancer patients unlikely to respond to EGFR-targeted therapies can be identified,' said Dr. Di Nicolantonio. 'This work has major potential clinical implications. Once prospectively validated, our results could immediately turn into molecular tests to be used in clinical practice.'

*Robert Day-Webb*

## Anti-tobacco campaigner wins lifetime award

*Professor Judith Longstaff Mackay*, a consultant to the World Health Organization (WHO) who was instrumental in developing the WHO's Framework Convention on Tobacco Control (FCTC), has won a Lifetime Achievement Award. Now working for the World Lung Foundation, she is part of the Bloomberg Initiative to reduce tobacco use in low and middle income countries.

She received the BMJ (British Medical Journal) Group Award in London in April 2009, where she was praised for her tireless and courageous campaigning on behalf of patients and public health care. In 1984, she started campaigning against the tobacco industry in Asia and 5 years later was labelled 'one of the three most dangerous people in the world' by the industry.

Speaking after the ceremony, Professor Mackay said, 'Public health has always been the poor relation to curative medicine when it comes to funding and recognition. This award is therefore a great acknowledgment of the importance of public health in general, and tobacco control in particular.

'I think my biggest contribution has been motivating and supporting others, moving tobacco control in low income countries from the very lonely job of a quarter of a century ago to one today involving hundreds of people. I have been overwhelmed by the support from so many organisations and colleagues internationally and especially from Asia and Hong Kong.'

More than 162 countries are now signed up to the WHO's FCTC, which places governments under international obligation to implement tobacco control policies.

## Acrylamide 'not linked' to lung cancer risk

Dietary acrylamide was not associated with increased lung cancer risk in men in a study in the Netherlands. In women, there was an inverse risk, so that those with the highest intake had the lowest risk of the disease. The researchers speculate that acrylamide may affect hormonal balances, which could explain how it reduces lung cancer risk in women, while increasing risk of endometrial and ovarian cancers (*J Natl Cancer Inst 2009;101:651–662*).

Acrylamide forms in some starchy foods during high-temperature cooking. Epidemiological studies have found a positive association between dietary intake and the risk of endometrial, ovarian, renal cell, and oestrogen-receptor positive breast cancers.

The Netherlands Cohort Study on Diet and Cancer included 58,279 men and 62,573 women, who completed food-frequency questionnaires upon enrolment. After a follow-up of 13 years, 1600 men and 295 women were diagnosed with lung cancer. Participants were divided into 5 groups according to their acrylamide intake.

In men, there was no statistically significant difference in lung cancer incidence in men who consumed the highest and lowest amounts of the chemical. By contrast, women with the highest intake had a statistically lower incidence of lung cancer, compared with those who consumed the least. All analyses were adjusted for smoking.

'This finding suggest that acrylamide is involved in human carcinogenesis through pathways other than genotoxicity,' the authors write, hypothesising that it may affect hormonal balance.

An accompanying editorial (*J Natl Cancer Inst 2009;101: 618–621*) expresses caution about any protective effect in women, pointing out the potential for false-positive associations.

Speculation about potential mechanisms should await confirmation of the association in additional studies, it states: 'Perhaps the safer conclusion... is that the findings do not support a positive association between acrylamide intake from diet and risk of lung cancer.'

# Cord blood transplants 'on the increase'

Adults with haematological malignancies are increasingly likely to benefit from cord blood transplants from unrelated donors, according to speakers at the European Group for Blood and Marrow Transplantation (EBMT)'s 35th Annual Congress (Gothenburg, Sweden; 29 March–1 April, 2009).

Encouraging results from a French study suggest that use of unrelated cord blood transplantation (UCBT) may broaden the application of transplant therapy to those previously excluded on the basis of age and absence of a HLA-matched unrelated donor. A second, pan-European study explored possible advantages of using intrabone, rather than intravenous transplantation.

Discussing the results with *EJC*, Professor Dietger Niederwieser, President of EBMT, stressed that the use of cord blood is not a first-line approach. 'You do a cord blood transplant where you can't find a matched donor. It's a new technique and the advantage is that the match does not have to be perfect. But while we have carried out about 35,000 standard bone marrow transplants in Europe, we have only done about 600 using cord blood.'

The first cord blood transplant was carried out 15 years ago and the technique has improved since then. The number of cord blood cells that can be harvested is small and initially the approach was thought to be only suitable in children because of their smaller body size: normally, a certain number of cells/kg of body weight is given. However, developments such as use of two cord blood transplants in a single recipient have increased the available dose.

*'TRANSPLANTS ARE GETTING SAFER; THE FIELD HAS ADVANCED ENORMOUSLY'*

Cord blood is not routinely collected, though there are cord blood banks now in the States and in Europe. Professor Niederwieser said that Spain, Italy, France and other Mediterranean countries were using much more cord blood than others. 'I think this approach has a lot of potential,' he said. 'If we had much bigger banks, we could have easy access to more grafts and donors. It will take money, and time, but I can see that activities in this field will increase considerably.'

*Professor Dietger Niederwieser*

The French study, presented by Dr. Bernard Rio (Unité de greffe de moelle, Hôtel Dieu, Paris) analysed 155 consecutive UCBT carried out in 21 French centres between 2003 and 2007. The recipients had a median age of 47 years. In the study group, 69 had myeloid and 22 lymphoid acute leukaemias (59%); the others had non-Hodgkin's lymphoma, myelodysplastic syndrome Hodgkin's disease, chronic myeloid or chronic lymphocytic leukaemia. At the time of the transplantation, 20% of the patients had active disease (*Proc. EBMT 2009 # 107*).

Overall survival of the patients at 18 months was 62%; disease-free survival was 51%. Remission of disease at the time of transplantation, and HLA (human leukocyte antigen) compatibility both increased disease-free survival (DFS). In fact, DFS was 70% for patients given a 6/6 or 5/6 HLA match, compared to 42% among those – the majority of the patient group – who received a UCBT with $\leqslant$4/6 compatibility.

Despite this, the researchers say their findings support the use of this approach 'as a strategy for broadening the application of transplant therapy to those previously excluded on the basis of age, and absence of a HLA matched unrelated donor.'

Dr. Francesco Frassoni (San Martino Hospital, Genoa, Italy) presented the second study which injected the cord blood directly into the bone, rather than being given intravenously. The idea was that it might reduce the rejection rate and that fewer cells might be needed, since some are normally lost as they circulate round the body.

The study was small, involving 50 matched pairs of adults given cord blood either intravenously or intrabone. Platelet recovery was better at day 60 among those receiving the intrabone marrow (IBM) transplants; strikingly also, incidence of acute graft versus host disease (aGvHD) was 12% in the intrabone group, compared to 38% in the intravenous group. Overall survival at one year was 67% compared to 43%, respectively (*Proc. EBMT 2009 # 106*).

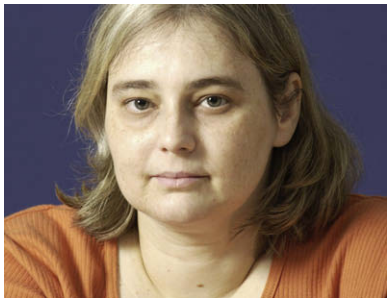
'Injection of cord blood cells via intrabone marrow seems to be able to overcome the problem of delayed platelet recovery observed after intravenous transplantation,' Dr. Frassoni said. 'The reduced incidence/severity of aGvHD observed in IBM patients is intriguing and promising.'

Professor Niederwieser said that, overall, progress is encouraging, especially for older patients with leukaemia: 'Every year, we have more experience with bone marrow transplants, and not just with cord blood.'

*Helen Saul*

# PODIUM

## MINDACT: Complex trials 'are feasible'



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*Dr. Fatima Cardoso is Assistant Professor in Medical Oncology (Jules Bordet Institute, Brussels, Belgium) and Scientific Director of the TRANSBIG network. Along with Professor Martine Piccart (Jules Bordet Institute) and Professor Emiel Rutgers (Netherlands Cancer Institute, Amsterdam), she is a co-Principal Investigator of the MINDACT trial. The results of a pre-planned pilot phase were released in March, 2009.*

**What is the MINDACT trial?**
This trial has the potential to be extremely important and change the way we treat cancer. MINDACT (Microarray In Node-negative and 1–3 positive lymph node Disease may Avoid ChemoTherapy) is exploring whether the 70 gene signature (MammaPrint™) can assess risk of relapse more accurately than clinico-pathological methods in early, operable, breast cancer.

Risk of relapse is assessed by standard clinico-pathological characteristics (age, lymph node involvement, grade, presence or absence of hormone receptors and HER-2) and by the genomic test. Where both tests suggest the risk is high, chemotherapy is recommended; where both suggest low risk, chemotherapy is not given, and the patients in the central group of discordant cases (one method suggests high risk, the other, low risk) are randomised to follow the clinico-pathology or the genomic recommendation.

**Why was the pilot phase necessary?**
To check that this complicated, new type of trial is feasible. An independent data monitoring committee looked at results from the first 800 patients to ensure that we did not have any major problem with protocol violations.

Sceptics initially said that neither patients nor investigators would be confident enough to allow the randomisation to decide whether or not chemotherapy would be given. They also thought that the real-time collection and analysis of frozen tumour samples in a multi-centre international trial would not be feasible: in the US frozen materials are not generally collected, not even in large clinical trials.

**What did the pilot find?**
That it is feasible to collect frozen material in a multinational trial. This had already been done by German colleagues who analysed uPA/PAI-1 from frozen material in 2 earlier trials. In MINDACT, our centres sent frozen material to a central laboratory in Amsterdam, and the results were back with investigators in 5–10 days, so that decisions on chemotherapy could be based on test results. It was a huge advance to prove we can do that. Collecting frozen material is no more difficult than using paraffin; it just means changing habits and adapting the logistics in the hospital.

The second main message was that the compliance rate was even higher than we expected, at around 95%. Both patients and physicians trusted the test, which is crucial.

**How many patients will be included in MINDACT?**
6000 in all. We now have 1400 patients in 63 centres in 9 European countries and we are adding about 120 more a month, which means recruiting until 2012. But we aren't yet at full strength; more centres are due to open, and our aim is to reach 150–200 new patients per month so that the trial will be finalised by the end of 2011.

**How representative of clinical practice is the trial protocol?**
The central lab ensures a very high quality of genomic test but this would change if the test were to be applied in clinical practice. We're also performing a central pathology review, although local pathology is used for treatment-decision making. Apart from these quality control measures, patients in MINDACT are representative of current clinical practice.

**How difficult is it for a centre to participate?**
Centres have to reorganise themselves into multidisciplinary teams with close collaboration between surgical, medical oncology and pathology departments, among others, so that patients can be informed about the trial before they have their breast surgery, and the results returned before they see their medical oncologist for discussion about systemic treatment. Some investigators say that joining the trial was a good excuse for reorganising multidisciplinary working, which should be done for every patient anyway.

**Did the pilot highlight any problems?**
More clinical low risk patients are being included than we'd estimated, but this is changing as time evolves and investigators become more confident; further, because we now include patients with node positive disease, the percentage of high clinical risk patients is steadily increasing. These patients can benefit the most from MINDACT since they would normally receive chemotherapy but the genomic test may allow them to be safely spared it.

**What has happened to the sceptics?**
Some have changed their minds and joined the trial. Others will only be convinced by results. We were discouraged at times and thought we were alone in believing in the genomic test. But things evolve quickly in medicine and people are much more at ease with genomic signatures than 5 years ago. Views have become less extreme in both directions; genomic tests aren't going to put pathologists out of work. This is an important new tool, to be incorporated with all the others.

*Helen Saul*