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Spotlight on Childhood Cancer

The International Union against Cancer (UICC)'s World Cancer Day 2006 was dedicated to childhood cancer. Activities and fundraising events were organised under the slogan "My Child Matters", with the aim of improving early detection by educating parents about common signs and symptoms of childhood cancer.

UICC launched 14 projects in 10 low- and middle-income countries on World Cancer Day. The projects will help improve early detection, treatment, care and support of children with cancer. The chosen countries are Bangladesh, Egypt, Honduras, Morocco, Philippines, Senegal, Tanzania, Ukraine, Venezuela and Vietnam.

Dr. Franco Cavalli, Chair of the UICC Childhood Cancer Campaign Advisory Committee, said, "In developing countries, where over 80% of children with cancer live and survival rates are lowest, governments have limited funding for health projects. These projects will help communicate the message that childhood cancer can be treated and is often curable."

Also on World Cancer Day, UICC launched a report, *Childhood Cancer: Rising to the Challenge*. It notes that childhood cancer is the second highest cause of death in children and more than 160,000 children are newly diagnosed with cancer each year. In developing countries, roughly 60% of children with cancer still die of their disease, as opposed to 25% in the developed world.

UICC© Photographer brian@le-studio.ch

The key image for World Cancer Day. The handprints represent the many children with cancer. The child's happiness is a symbol of hope and life if childhood cancer is detected early.

Significant advances in diagnosis and therapy during the past four decades mean that childhood cancer can largely be cured if detected early. Isabel Mortara, Executive Director, UICC, said, "Too many children are unnecessarily dying each year, since they are never diagnosed or diagnosed too late. Knowing the common signs and symptoms of childhood cancer is one of the most important steps in fighting this disease."

Supporters of World Cancer Day include former US First Lady, Barbara Bush, football stars, Franz Beckenbauer and Gary Lineker and World Figure Skating Champion Stéphane Lambiel.

Insecticides and leukaemia

Household insecticides may increase the risk of acute leukaemia in children, say French researchers (*Occup Environ Med 2006*;**63**:131–4). Children exposed to insecticides in the garden, house or to treat head lice, had approximately double the risk of those who had no contact.

The case controlled study included 280 children newly diagnosed with acute leukaemia and 288 healthy controls. In detailed face-to-face interviews with mothers, researchers asked about insecticide use during pregnancy and in the period between birth and diagnosis.

Household and garden insecticides, along with insecticidal shampoos used to eradicate head lice, were all associated with increased risk, but the researchers said no one agent could be singled out. "The observed association with insecticidal shampoo treatment of pediculosis, which has never been investigated before, requires further study," the authors say.

The report concluded, "A causal relation remains questionable. However, the consistency of our results, and the results from previous studies suggests that it may be opportune to consider preventive action".

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DNA repair mystery "solved"

UK scientists believe they have found the final protein involved in a type of repair of severe DNA damage (*Cell 2006;***124**:2).

The repair pathway, called non-homologous end joining, is crucial for protecting cells and reducing the chances that they will become cancerous. Professor Steve Jackson (Cambridge University, UK) found the first component of the process 10 years ago. In the meantime, scientists thought they had mapped out the process until further evidence suggested a step was still missing.

Peter Ahnesorg, one of Professor Jackson's PhD students, "went fishing" for the missing molecule. He used an established component of the repair pathway as "bait" and cast it into a sea of proteins. Then he pulled out the bait and examined what was stuck to it.

Professor Jackson said, "As well as catching the usual debris and old boots, we had what looked like a real fish, a molecule that hadn't ever been studied before. And now we've confirmed it is, in fact, the missing part of the jigsaw."

The molecule is called XLF (XRCC4-like factor) and, while it may have a role in causing cancer, it could potentially also be targeted by new cancer treatments. For example, blocking the action of XLF in cancer cells might increase the effectiveness of radiotherapy.

Professor John Toy, medical director of Cancer Research UK, said he hoped the discovery could be exploited in the search for improved treatments. "The XLF molecule may complete our understanding of this DNA repair process, and the new knowledge about this protein can hopefully be used to improve cancer therapy."

Researchers find Singapore difficult to resist

Singapore has recruited leading international researchers such as Neal Copeland and Nancy Jenkins from the USA and scientist Alan Colman from the UK, among others, to kick start the development of a billion-dollar bio-medical industry.

In the USA and Europe, the climate for researchers can be tough, with fierce competition for grants and many restrictions on commercial exploitation. However, Singapore is different—there is plenty of money available for biomedical research and drug production, and a high level of interest in commercial applications of research.

Moreover, Singapore is winning business from other countries in Asia. For example, in January, 2006, GlaxoSmithKline said it might now turn to Singapore rather than South Korea to build a US$300 million research centre for the development of raw materials for influenza vaccines. GlaxoSmithKline said Singapore recently came up with a better offer, and would listen to all the company's requirements, including their location needs.

David Heenan, an eminent US businessman and academic, published a book *Flight Capital: The Alarming Exodus of America's Best and Brightest* in October, 2005, which addresses what is happening in countries such as Singapore. "This is one of the world's great economic success stories", he notes.

Towards the end of the 1990s, *Contact Singapore* was set up to locate and poach global talent. "Many eminent scientists born in Singapore have been persuaded to return, including Edison Tak-Ban Liu, a scientist trained at Stanford University, San Francisco, CA, USA, who traded in his directorship at the US National Cancer Institute, Baltimore, MD, USA, to head the Genome Institute of Singapore", Heenan continues.

Now the USA is losing its own researchers because of more favourable research conditions elsewhere: "On its present course, America's nation of immigrants could become a nation of emigrants", predicts Heenan.

Kathryn Senior

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European approval for topotecan

The European Commission has granted marketing authorisation for intravenous Hycamptin (topotecan) for the treatment of patients with relapsed small cell lung cancer (SCLC). This follows a positive opinion in November 2005 from the European Committee for Human Medicinal Products (CHMP).

Topotecan is already registered in the European Union, and 59 other countries, for the treatment of relapsed ovarian cancer following platinum-based therapy. It is a topoisomerase I inhibitor which interferes with the replication of DNA, and therefore cell division, in both normal and cancer cells.

The EC's approval was based on three phase III studies; one of which showed it provided greater symptom improvement than the triple combination cyclophosphamide, doxorubicin and vincristine (CAV).

Investigator Dr. Joachim von Pawel (Asklepios Kliniken München-Gaunting, Germany) said it showed no neurotoxicity and patients experienced a significant improvement in breathing difficulties and anorexia. It improves the quality of life for patients "and essentially allows them to make the best use of the time they have left."

Cauliflower, broccoli and DNA repair

A molecular mechanism has been proposed to explain how broccoli, cauliflower and cabbage may protect against cancer. US researchers have shown that the I3C (indole-3-carbinol) found in these vegetables, along with genistein in soybeans, increase levels of DNA repair proteins.

The researchers, based at Georgetown University, Washington, DC, found that both compounds acted to boost levels of BRCA1 and BRCA2 proteins *(Br J Cancer 2006;***94**:3). The decreased levels of these proteins in people with faulty BRCA genes puts them at increased risk of developing certain cancers; higher levels of the proteins might therefore prevent cancer developing.

Lead author Professor Eliot M. Rosen, said that, despite epidemiological evidence that eating certain vegetables might protect against cancer, the mechanism of action has not previously been pinned down. "Before we can say a food protects against cancer, we have to understand how it does this at a molecular level.

"It is now clear that the function of crucial cancer genes can be influenced by compounds in the things we eat. Our findings suggest a clear molecular process that would explain the connection between diet and cancer prevention."

Drug discovery collaboration

The genomics-based drug discovery company Galapagos (based Brussels, Amsterdam and London) has joined forces with Cancer Research Technology, CRT (a wholly owned company of Cancer Research UK). Under the terms of the agreement, Galapagos' service division BioFocus will provide medicinal chemistry services on a series of CRT anticancer drug programmes. In return, CRT will fund the work of four BioFocus scientists throughout 2006.

Tony Raynham, CRT's Head of Medicinal Chemistry, said that the collaboration, along with in-house resources, will ensure that anticancer programmes "are advanced rapidly through early-stage development, thereby creating robust licensing opportunities and cancer patient benefit."

The Advance of the TKIs

The US's Food and Drug Administration (FDA) has announced approval of sunitinib (Sutent), for the treatment of gastrointestinal stromal tumours (GIST), and advanced renal cell cancer (RCC). This follows the FDA's recent approval of sorafenib (Nexavar), also for RCC (*see EJC News, 2006;***42***:4*).

Sunitinib, from Pfizer, is a tyrosine kinase inhibitor (TKI); sorafenib, from Bayer, a multi-kinase inhibitor which targets serine/threonine as well as receptor tyrosine kinases.

''THESE ARE NOT ME-TOO DRUGS''

Both new agents act through multiple targets known to be involved in both tumour cell proliferation and tumour angiogenesis. The drugs are taken orally.

Dr. Bernard Escudier (Institut Gustave Roussy, Villejuif, France) said the drugs are important. "They are going to completely change the way we treat renal cancer," he said. Renal cancer is sometimes considered an orphan disease, but affects 35,000 people in Europe. Further, he said, "It is a very good model for the development of anti-angiogenesis drugs."

Dr. Thomas Hutson (Baylor University Medical Center, Dallas, TX, USA) also specialises in treating RCC and said that the two drugs were a "major advance" in treating the disease. They target some of the same pathways but there are sufficient differences in their actions to mean they are not "me-too" drugs. Both inhibit VEGF and PDGF kinases, but sorafenib also targets ras and erk pathways, where sunitinib targets ckit and ret. "It's a reasonable belief that if one does not work, the other will," he said.

He stressed that the drugs are not the same. "They have different response rates and the side effects, though similar, differ in severity." The Glivec story implies that resistance to these agents may become a problem. Dr. Hutson said the mechanisms leading to resistance need to be further qualified. On-going prospective studies are examining the development of resistance to the drugs, and results are expected over the next year. In the meantime, Dr. Hutson said that it has been observed that, where a patient receiving one of the drugs experiences tumour progression, the other agent may still retain some activity. "It suggests that other pathways are involved," he said.

Both drugs were approved rapidly by the FDA. Data on overall survival were available for sorafenib, but sunitinib was approved on the basis of alternative endpoints. Interim analysis of a trial in GIST found that treatment with sunitinib increased time-to-tumour progression from 6 weeks (among those who did not receive the drug) to 27 weeks. Its approval for the treatment of advanced RCC was based on its ability to delay the growth of tumours.

Announcing the FDA's approval of sunitinib, Dr. Richard Pazdur, Director of FDA's Office of Oncology Drug Products, said "Today's approval of this drug for these indications provides compelling evidence that the use of alternative data endpoints allows us to see the benefits of novel therapies earlier in patients."

The mechanism of action of many new and emerging treatments is to delay tumour progression, rather than to shrink the tumour. Dr. Escudier said the use of alternative endpoints is therefore appropriate,

''THEY WILL COMPLETELY CHANGE THE WAY WE TREAT RENAL CANCER''

especially where there are few alternatives: "It is a good thing when we have a real need for new drugs".

Dr. Hutson pointed out that the drugs were approved for first line therapy, despite the lack of data comparing their effectiveness with traditional treatment strategies (interleukin-2 and interferon). A phase III trial comparing sunitinib with interferon has completed accrual and an interim analysis is expected to be presented at American Society of Clinical Oncology (ASCO) 2006. However, Dr. Hutson said that the FDA had decided it is not in patients' best interests for them to have to receive traditional therapies before starting on the new drugs. "It would be inhumane to force patients to receive minimally effective traditional therapies before being allowed the new therapies. We know, historically, that only a minority of patients benefit from the traditional treatments, and they are very toxic," he said.

He stressed the difference the drugs could make to patients. "We have had several patients on sunitinib for 2 years or more, enjoying a quality of life they would not have achieved if the drug had not been available to them. One – a policeman – was still working with advanced RCC. This would never have been possible without the drug."

Approval in Europe may still take time. Dr. Escudier said he expects that surrogate markers will be accepted increasingly, but he expects that the European Medicines Agency (EMEA) will lag behind the FDA in this regard. "The EMEA is not as active as the FDA because Europe is a mixture of many countries with many different sensitivities, which is why change takes so long. The economic implications of approving a drug are much more important in Europe than in the US. The FDA does not have to take responsibility for economic issues; they are seen as problems for health insurers."

In the US, an expanded access programme for sunitinib prior to approval made the product available to patients outside of clinical trials and currently, more than 1700 patients are receiving the drug through this programme. Ellen Stovall, President of the US' National Coalition of Cancer Survivorship said, "There needs to be a greater awareness among patients and doctors about both the option to participate in clinical research as well as in these expanded access programmes in order to make promising new therapies available to as many patients as possible."

Dr. Escudier said the new drugs would be very expensive and European countries will struggle to meet the increasing costs of cancer care. New targeted agents tend to be useful in a range of tumour types, and are often given in combination with other treatments, thus increasing the costs. "It will be the same with these agents," he said.

Both sorafenib and sunitinib were due to be discussed at a meeting of the EMEA Scientific Advisory Committee on March 9th, 2006.

Air filtration 'intended to circumvent smoking bans'

Newly released documents reveal that, despite knowing that ventilation and air filtration are ineffective at removing environmental tobacco smoke, British American Tobacco (BAT) promoted these technologies to the hospitality industry as viable options to smoking bans.

An article (*BMJ 2006*;**332**:227–9) based on documents made available as a result of litigation against tobacco companies, states that BAT itself found in 1993 that air filtration units were only 34% efficient at removing particulate matter from cigarette smoke. The units significantly reduced particulate matter that could be seen and smelled, but did little to remove harmful gas phase smoke constituents including carbon monoxide and volatile organic compounds. BAT installed these units worldwide, and in some cases, the units themselves were branded with cigarette advertising.

BAT targeted the hospitality industry by pushing a so-called "smoker resocialisation" initiative, which aimed to portray smoking in a "more positive and stylish context" and to lobby against smoke-free public places.

BAT scientist Nigel Warren described the "perceived effectiveness" of these units, when demonstrated to hospitality managers, according to the *BMJ* paper. Warren stressed that the introduction of filtration and ventilation was to be portrayed as a strategy for accommodating smokers and non-smokers together. "[We] don't want to imply that BAT's goal is to try to overturn smoking bans."

However, Warren also described "smoking tables" in a bar at Birmingham International airport, UK, which suck tobacco smoke down through a filter and recirculate the partially filtered smoke back into the room. Their introduction apparently led to a reversal of the smoking ban in the airport.

The authors of the *BMJ* report call on the public health community to reject the UK Government's proposal to allow smoking to continue in private clubs and pubs that do not serve food. "Without a comprehensive smoke-free workplace law, the tobacco and hospitality industries can continue to mislead the public about the hazards of exposure to environmental tobacco smoke by promoting separate seating, ventilation, and air filtration as viable options to smoking bans," they say.

Palliative radiation 'cures' NSCLC

About one in 100 patients with apparently incurable non-small cell lung cancer (NSCLC) survive 5 or more years after being given relatively small doses of radiation, say Australian researchers (*Cancer 2006 DOI:10.1002/cncr.21704*).

Physicians have long observed that some patients receiving palliative radiotherapy live for years more than their estimated survival. There are even rare reports of cures.

Radiation oncologist Dr. Michael MacManus (Peter MacCallum Cancer Centre, Melbourne, Australia) and colleagues followed 2337 patients with confirmed and apparently incurable NSCLC. All had received palliative dose radiotherapy.

Approximately 1.1% survived 5 or more years, including 18 who achieved an apparent cure. These patients were more likely to have higher functional scores at diagnosis, and less likely to have metastatic disease compared to patients who lived less than 5 years. However, there were no other conventional prognostic factors to predict survival with palliative dose radiotherapy.

A subset of patients appears to have disease that is curable with minimal therapy. This may explain occasional cures attributed to unconventional therapies or faith healing, the report concluded.

"Our data show that close to 1% of patients with NSCLC have prolonged survival with doses of palliative radiotherapy that would not normally be considered for long term disease control," the researchers said. Future studies should focus on identifying patient characteristics because "prospective identification of such patients could potentially profoundly influence treatment."

Ethnic differences in smoking-related risk

African Americans and Native Hawaiians are more susceptible to smoking-related lung cancer than whites, Japanese Americans and Latinos, according to US researchers (*NEJM 2006*;**354**:333–42).

The prospective Multiethnic Cohort Study enrolled 215,000 men and women in California and Hawaii between 1993 and 1996. Researchers used the Surveillance, Epidemiology and End Results (SEER) cancer registries to identify 1979 cases of incident lung cancer over the 8-year period up to 2001.

Among those who smoked no more than 30 cigarettes per day, African Americans and Native Hawaiians had significantly greater risks of lung cancer than those in other groups. Differences were not significant among heavier smokers. The effect was not explained by risk factors such as diet, occupation or socioeconomic status.

The researchers suggest that differences in the metabolism of nicotine and tobacco carcinogens may help explain the finding. African Americans and Native Hawaiians may be "constitutionally more susceptible to the effects of tobacco carcinogens".

Unplanned attempts to quit "more likely to succeed"

Unplanned attempts to stop smoking are more likely to succeed than planned ones, London researchers say (*BMJ* online 2006).

Planning has been thought to be important in smoking cessation but the study, based on interviews with 1900 smokers and ex-smokers in England, found unplanned quit attempts were more likely to succeed, even after adjusting for age, sex and socioeconomic group.

The authors say that their findings do not necessarily imply that planning is counterproductive: use of behavioural support and nicotine replacement therapy – which generally require forward planning – are known to improve the chances of success. "More likely, whether a quit attempt is planned or unplanned reveals something about the state of mind of the smoker at the time, which has importance for whether the attempt will last.

They suggest an alternative model, based on catastrophe theory. Smokers have varying levels of motivational tension to stop, when a trigger in the environment leads to a sudden renunciation of smoking.

Public health campaigns could focus on the "3 Ts": creating motivational tension, triggering action in smokers who are on the cusp of a change in their orientation to smoking, and immediate availability of treatment such as nicotine patches and counselling.

PODIUM

Inflammation: a double-edged sword

Professor Fran Balkwill

*Fran Balkwill is Professor of Cancer Biology at Barts and The London, Queen Mary's Medical School, UK. She studies the links between cancer and inflammatory disease, in particular the role of inflammatory cytokines in cancer promotion. She is actively involved in communication of science to non-specialist audiences, especially children, and received the 2005 Royal Society Michael Faraday Prize in recognition of this work. She is the guest editor of EJC's forthcoming Special Issue on Inflammation and Cancer, 2006;***42**(6).

How far back does the study of inflammation in cancer go?

It's been known for a long time that tumours have lots of infiltrating cells. Tumour immunologists held sway for years with the view that all these cells are a specific immune response against the cancer. It is not terribly logical since cancers can be so aggressive.

What has sparked recent interest?

The observation from several laboratories that tumours actively recruit and then subvert inflammatory cells. The infiltrating cells, far from attacking the cancer, help it to grow and spread. I was inspired by Harold Dvorak's description of tumours as wounds that do not heal *(NEJM 1986;***315***(26):1650–9)*. There are some data backing the idea of immune surveillance (in which the immune system normally mops up cancer before it causes trouble) but by the time you see an advanced cancer, any specific immune response has been suppressed.

How closely linked is cancer and inflammation?

The cells and processes associated with chronic inflammation are found in human cancers, as we've said. Further, cancer arises in sites of chronic inflammation. Then, in the last 10 years, we've become aware that if you inhibit various inflammatory cells and soluble mediators of inflammation, you inhibit the development of experimental cancer. Finally, large population-based studies over a long period of time have established that long-term use of non-steroidal anti-inflammatory drugs can protect against mortality from bowel cancer and possibly other cancers.

How might inflammation influence the development of cancer?

Inflammation may do different things at different stages, but most data suggest it is involved early on. If an initial genetic lesion arises in the presence of chronic inflammation from another source, the inflammation may promote further genetic damage and proliferation of the transformed clone of cells. In other cases, the genetic lesion may itself provoke inflammatory stimuli: a mutation in *ras* leads to overproduction of interleukin-8, for example.

What are the most exciting areas of research?

We're trying to understand and define the nature of chronic inflammation in cancer, and how it relates to acute and chronic inflammation in other diseases. We're looking for the targets and mechanisms by which this inflammation promotes cancer growth and spread.

What are the implications of the work?

There is a strong translational aspect. If inflammation promotes cancer growth and spread, inhibiting it may have an impact on cancer. The questions being asked in basic cancer biology are: Why are all these cells there? Why are cancer cells not just cancer? How does that happen? But the second line of thinking is: How can we exploit this and develop new therapies to complement existing treatments?

There have been problems with early attempts to use the theory in the clinic.

Yes, but the cancer field will recover from the problems with Vioxx and the COX-2 inhibitors. There are many other ways of targeting pathways and ongoing clinical trials are exploring these. It's also possible that some successful cancer drugs may not just be targeting tumour cells. They may have knocked out tumour-associated macrophages for instance. There's a lot to discover.

So in the age of targeted treatments, drugs still work through unexpected mechanisms?

Cancer cells mutate and therefore they are moving targets. You target one pathway successfully, but some cells return having found another pathway, and having become resistant to your treatment. But if, when you give the targeted treatment, you also make the environment incredibly hostile, you may have more impact. It's a two-pronged attack: you don't just kill the cancer cell, you kill its environment.

Are drugs targeting inflammation always likely to be used in conjunction with other agents?

My view is that treatments which target inflammation are more likely to slow down or stop recurrences of cancer. If chemotherapy or a targeted treatment compromises cancer cells, anti-inflammatory drugs take away their support system.

What is the take home message for non-specialists?

That cancer is not just a mass of malignant cells: half or more of the cells in a cancer are normal cells. We hope we'll be able not only to suppress harmful chronic inflammation and prevent recurrences of cancer, but also to allow specific and helpful immune responses to happen.

What do you hope the Special Issue will achieve?

I hope it will increase awareness of the research, and let readers know that it is becoming important and interesting. I hope it gives cancer specialists ideas, and that these ideas permeate the field. Oncologists may come up with applications and observations that we in the lab don't have.