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No new cancer genes found in human genome

The first draft of the human genome sequence has not uncovered novel cancer genes, say cancer geneticists (*Nature* 2001, **409**, 850–852). A group led by Professor Michael Stratton (Institute of Cancer Research, Sutton, Surrey, UK) concluded that the draft ''will not immediately reveal the natures of the abnormalities in cancer cell genomes''.

The human genome sequence was published in the same week by the two rival teams: the publicly funded International Human Genome Sequencing Consortium (*Nature* 2001, **409**, 860–921) and biotech company, Celera Genomics (*Science* **291**, 13.4–1351). ''The human genome holds an extraordinary trove of information about human development, physiology, medicine and evolution,'' writes the International Consortium. However, much work remains to be done before its applications in cancer genetics can be realised.

"AN EXTRAORDINARY TROVE OF INFORMATION."

Professor Stratton's group used a two-pronged approach. They first searched for paralogues of known tumour suppressor genes, but found none. They then searched directly for oncogenic sequence changes in cancer cells by comparing cancer genome sequences against the draft genome. However, they found a similar level of these changes in both normal and cancerous tissue, emphasising the level of false-positives. "Our experiment underscores the limited amount and variable quality of DNA sequence from cancer cells that is currently available," they write.

The search for novel paralogues may have been unsuccessful because most have already been found, but the researchers say that, given the striking diversity of structure and function of cancer genes, this may not have been a useful way of generating likely candidate genes. "Hardly any of the known recessive oncogenes have strong homology to any other," they say. "We may learn more about the mutations driving cancer if we are not too heavily influenced by past experience."

"THIS IS A DAUNTING CHALLENGE."

The second approach used the genome sequence as a template against which structural alterations of the genome in cancer cells could be detected. However, there is little cancer genome sequence available at present. "Elucidating the complexity of cancer at the genomic level will require much more sequence data from cancer genomes," they say.

The finished sequence will be needed before massive-scale comparisons of cancer cell and normal genomes can be carried out, the researchers say, but add that, ultimately, systematic genome-wide searchers for mutations will be possible. New technology will be required and genomic libraries constructed from cancer genomes will be sequenced. They conclude, "Given the diversity of cancers and the effort and cost required to obtain reasonable coverage of a human genome, this is a daunting challenge".

Next step: Human Proteome Project

Improved understanding of proteomics is the 'next logical step' after sequencing the human genome, according to the newly formed Human Proteomic Organisation (HUPO). "Whilst the genome is fundamental in providing the building blocks of Life, it is the proteins that do the work," says HUPO.

Proteomics is the study of the function, regulation and expression of proteins in the normal cell and in the initiation or progression of a disease state. Professor Sam Hanash (University of Michigan, USA), an inaugural council member of HUPO said, "In the field of cancer research, proteomics will very likely fill an unmet need for reliable markers that allow early diagnosis to be made. Also, proteomics will likely provide a multitude of novel targets for chemoprevention and therapy, as we understand the role of protein modifications and protein–protein interactions in diseases."

HUPO aims to increase awareness of proteomics across society, particularly of the Human Proteome Project, to foster international cooperation across the proteomics community and to promote ongoing scientific research around the world.

The inaugural meeting will take place in Virginia, USA, 2–4 April 2001. Contact Chris Spivey, Cambridge Healthtech Institute (Tel.: +1-617-630-1373; *e-mail address: cspivey@healthtech.com*) for further information.

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Childhood cancer: large variations in survival remain

Wide variations in survival from childhood cancer exist across Europe, according to EUROCARE, the largest European study on childhood cancer ever published. It included data on 45 000 children diagnosed with cancer between 1978 and 1992.

Finland, southern Sweden and western Germany had favourable outcomes for most cancers; as did Holland for leukaemia. Results in the UK, Denmark, Slovenia, France and Italy were mixed; and poor survival was repeatedly seen in Slovakia, Poland and Estonia. "Survival in Finland, Iceland and Sweden … seems to represent a gold standard to which all countries who devote similar resources and have comparable health systems can reasonably aspire," the authors say.

Results from EUROCARE will be published in a special issue of the *European Journal of Cancer* (Vol. 37, issue 6). Data came from 34 population-based registries in 17 countries and included cancers in children aged up to 14 years. This data represents between 35 and 40% of all newly diagnosed cases of cancer in Europe. The UK and West Germany provided most of it, 60%.

Five-year survival, adjusted for age and site was 75% in the Nordic countries compared with 66% in Denmark and the UK and 55% in Eastern Europe. Germany had survival rates of 72% and other Central and Southern European countries had 67%. Differences between Eastern and Western European countries "reflect huge economic and social inequalities within former socialist countries," the authors say. Improvements started later in these countries, in the mid-1970s, rather than in the mid-1960s in Western Europe. The EUROCARE data mainly describes survival during the late 1980s and early 1990s and they say, "Very likely, improvements may have been realised in the meantime."

The analysis found that mortality rates improved over the study period so that for most childhood cancer sites, survival in European children diagnosed with cancer in the late 1980s was similar to that in the US between 1985 and 1994. The authors say, "This is reassuring. In the field of paediatric oncology over the last half a century, the US have had a major role in the discovery and application of treatment innovations."

Overall, the authors attributed improvements in survival to effective multidrug chemotherapy regimes, supportive measures to overcome toxicity, megavoltage radiation and improved diagnostic techniques. "This has been a triumph of modern medicine," the authors say. For example, the 5-year survival rate from acute leukaemias, which account for most childhood leukaemias, increased from 20–30% in the 1960s to 60–75% in the 1980s and the authors say, "There is still some possibility of obtaining further improvement."

For the future, the authors suggest that attention must turn to quality of life issues. An extrapolation of figures from the UK and Italy suggests that at least 100 000 young people in Europe have overcome a childhood cancer. "At the beginning of the new millennium, therapeutic protocols, albeit effective, are still biologically aggressive: undesirable side-effects are commonly produced in a sizeable number of children being treated," they say. Population-based studies using cancer registries offers a "unique opportunity for achieving reliable estimates of an emerging public health problem," they say.

'No common cause' for colorectal cancer and IBD

Colorectal cancer and irritable bowel disease (IBD) do not appear to share a common cause, say Swedish researchers (*Lancet* 2001, **357**, 262–266). They found no increase in rates of cancer among 114 102 first-degree relatives of patients with IBD. ''These results offer little support for a common genetic susceptibility for IBD and colorectal cancer,'' they say.

IBD is known to be a strong risk factor for colorectal cancer and genetic susceptibility is important for both diseases. The researchers identified 5870 colorectal cancers among relatives during 3 048 488 person-years of follow-up which represents a slightly decreased relative risk. Only relatives of patients with IBD and colorectal cancer had an increased risk of the cancer themselves.

Relatives with IBD were excluded from analysis, which could partly explain the overall decreased risk of cancer. More speculative explanations include differences in diet between families with IBD and the general population. Alternatively a genetic trait could confer protection against colorectal cancer but increase susceptibility to IBD, the researchers say.

A related editorial (*Lancet* 2001, **357**, 246–247) states that colitis and colorectal cancer are more likely to have a cause-and-effect relation than to share a genetic link. This ''implies that optimum anti-inflammatory therapy will provide effective cancer prevention. Indeed, there is evidence that regular treatment with amino-salicylates reduces the risk of colorectal cancer in patients with ulcerative colitis,'' it states. It adds, ''Environmental factors such as smoking and the enteric bacterial flora may contribute to the pathogenesis of both processes.''

'No difference' between BL and BLL

Burkitt's (BL) and Burkitt-like (BLL) lymphoma may be different at morphological and molecular biological levels, but clinical features and outcome were the same in a small retrospective study among Greek adults (*Leukemia Res* 2000, **24**, 993–998). It included 11 patients with BL and 13 with BLL; all were HIV-negative.

Other studies have suggested that morphological differences may lack clinical importance. Analysis of a larger series of nonendemic BL will be necessary to clarify any difference between the two variants, the authors say. Until this has been done, all patients with small non-cleaved cell lymphoma (SNCL) should be treated uniformly with intensive protocols, they say. The disease in advanced stages is extremely aggressive and intensive treatment is "absolutely indicated".

NHL patients 'should not be subjected to high-dose chemotherapy'

Standard chemotherapy remains the treatment of choice for most patients with aggressive non-Hodgkin's lymphoma (NHL), according to an EORTC study (*J Natl Cancer Inst* **93**, 22–30). Researchers recommend that those at low or low-intermediate risk should not be subjected to high-dose chemotherapy with autologous bone marrow transplantation (ABMT) as a first-line therapy.

The randomised study was carried out by the EORTC lymphoma Group. It compared a standard polychemotherapy (cyclophosphamide, doxorubicin, teniposide, prednisolone with bleomycin and vincristine added at midcycle) with a high-dose chemotherapy (carmustine, etoposide, cytabarine, cyclophosphamide) coupled with ABMT. It found no significant difference in either time to disease progression or overall survival at 5 years.

The study included patients with aggressive NHL aged between 15 and 65 years who were followed for a median of 53 months. They received three cycles of polychemotherapy, and the 194 patients with a complete or partial remission were then randomised to receive either a high-dose chemotherapy coupled with ABMT or more of the same polychemotherapy.

Most of the patients in the trial, 70%, were of low or low-intermediate risk. Five-year survival in the treatment group was 68% compared with 77% in the control arm. The small numbers involved meant that this was not a statistically significant difference.

The researchers say that at the time the protocol was written, a 20% difference in time to disease progression at 5 years was expected in favour of the ABMT therapy. This would now be considered too optimistic. They add, "Alarming new data demonstrate a high incidence of secondary malignancies after ABMT procedures."

"Patients with IPI low risk or low-intermediate risk should not be submitted to bone marrow ablative intensification as initial therapy," they conclude. They suggest that high-risk patients may benefit, but say, "Only large intergroup randomised studies will be statistically powerful enough to give meaningful answers for the future."

The accompanying editorial (*J Natl Cancer Inst* 2001, **93**, 4–5) states that a US trial has been set up to compare early versus delayed high-dose therapy for patients with high-intermediate and high-risk lymphomas. These patients have a 5-year survival of only 32–46% with current therapy. ''If successfully completed, this trial should define whether ABMT has a role in the initial treatment of poor-risk patients with NHL,'' it concludes.

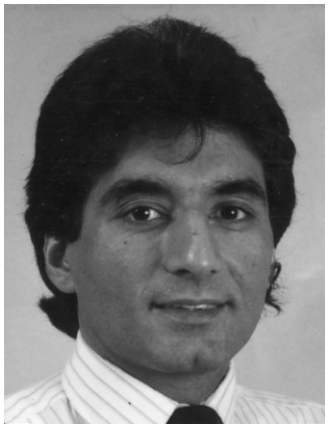
Major advance in CML treatment

Early clinical trials with a new drug for chronic myeloid leukaemia (CML) are extremely promising, says the co-author of a paper in this issue of *EJC*. Dr Tariq Mughal (Institute of Cancer Studies, Manchester, UK) said that the novel drug STI 571 can be given by mouth, reduces the leukaemic cell burden fairly quickly and appears to have no significant toxicity.

CML was regarded as inexorably fatal until the early 1980s when it was accepted that allogenic stem cell transplantation could cure some patients. Interferon-alpha (IFNα), either alone or in combination with cytarabine, became the non-transplant option of choice in the late 1990s when its potential to prolong survival was recognised. However, IFN often takes about 6 months to exert its effect, and most patients have side-effects, particularly flu-like illness and fatigue: "STI 571 can work within weeks," he said. Blood counts are normalised and cytogenetic responses are seen afterwards.

Although STI 571 appears to be effective, the drug has only been in clinical trials for just under 3 years and its potential to offer molecular remission has yet to be elucidated. Nevertheless, enthusiasm is such that the drug will probably be approved for use in the US later this year.

STI 571 targets the BCR-ABL oncoprotein, which is generally believed to be responsible for CML. It is an Ab1 tyrosine kinase inhibitor which was designed specifically to treat CML. It



Dr Tariq Mughal

selectively suppresses the growth of CML cell lines. An earlier study found that 90% of CML patients in chronic phase refractory to IFN obtained complete haematological responses with STI 571; 40–45% achieved cytogenetic responses. "If the responses are sustained and confirmed more generally, this novel drug will become the preferred non-transplant treatment option," the authors write. They say that the decision-making process to select the optimum treatment for CML has become exceedingly complex.

A number of international trials are currently in progress.

NICE work

The UK National Institute of Clinical Excellence (NICE), which aims to issue evidence-based guidance to the National Health Service, is to consider the use of STI-571 for CML. The Department of Health said, "The drug may provide an important new option for treating the disease, although some uncertainties remain."As part of the same programme, NICE will consider the use of Caelyx for ovarian cancer. It has already been asked to appraise other drugs in ovarian cancer, and, according to the Department, "This appraisal would ensure that clinicians had comparative guidance available on all the modern drugs to treat this condition."

Cancer 'switch' found in frog's eggs

A joint Scottish/French team have identified a 'switch' which controls cell division and may provide a new target for cancer drug development (*Nature Cell Biology* 2001, **3**). The researchers worked with the unfertilised eggs of the African pipid frog, *Xenopus*, but proposes that a similar switch also exists in human cells.

The researchers purified a component of the switch, known as RLF-B/Cdt1, which controls the process of gene copying. The protein geminin interacts with RLF-B/Cdt1, so that gene copying does not occur when geminin is present inside cells. When geminin is not present, gene copying can occur and cells can divide.

Geminin is normally degraded during late mitosis, but the researchers suggest that losing geminin altogether could be a crucial step in the development of cancer. This would leave the way open to uncontrolled cell growth. Drugs that work in the same way as geminin to prevent cell division could improve the prospects of cancer patients.

Dr Julian Blow (University of Dundee, UK) said the discovery was exciting. "If we could prove that the switch goes wrong in cancer, and find out how this happens, it might lead to new drugs to protect our cells from the disease."

Skin disease link with cancer confirmed

Patients with dermatomyositis have 3 times the normal risk of cancer, according to a study in northern Europe (*Lancet* 2001, **357**, 96–100). Researchers recommend that patients with this disease undergo thorough screening for certain cancers.

Analysis of pooled data from Sweden, Denmark and Finland included 618 cases of dermatomyositis, of whom 198 had cancer. Risk of ovarian cancer was increased 10-fold, risk of lung cancer increased almost 6-fold; other strong links were found with pancreatic, stomach and colorectal cancers and non-Hodgkin's lymphoma. Risk was highest in patients over 45 years old, but existed nonetheless among younger patients. Risk was also highest within the first year of diagnosis, and dropped off substantially over subsequent years.

The study also included 914 cases of polymyositis, of whom 137 had cancer. This represented a 30% increase in cancer risk, with the greatest increased risks for non-Hodgkin's lymphoma, lung and bladder cancers. The researchers say their work emphasises that "dermatomyositis and polymyositis are different diseases, in respect of the magnitude of risk and types of associated malignant disease."

"Dermatomyositis is probably a paraneoplastic event in some patients," they write, and add that it has been seen to improve after treatment of cancer. Recurrence of muscle weakness has also been observed at relapse of the malignant disease.

According to the researchers, current recommendations for cancer screening vary widely. "Our finding suggest that, in addition to routine examination and laboratory screening, chest computed tomography (CT) scan, faecal blood testing, abdominal ultrasound or CT scan; mammography, pelvic CT scan, or ultrasound, and gynaecological examination, are justified in those with dermatomyositis," they say. "Even if mortality is not prevented, or survival prolonged, for those malignant diseases, disability from myositis could be alleviated if cancers are detected and treated early enough."

An accompanying commentary (*Lancet* 2001, **357**, 85–86) notes that this study dealt only with white patients. Other work has suggested a link with nasopharyngeal cancer among Asians, and that the Nordic findings may not hold among patients of African or Mediterranean descent. ''Some form of search for cancer should be made in every patient with dermatomyositis, and should be planned individually, taking into consideration the patient's age, sex, and ethnicity,'' it states.

BRCA1 'related to poorer survival'

BRCA1 mutations are associated with reduced survival in women with breast cancer, say French researchers (*J Clin Oncol* 2000, **18**, 4053–4059). Their findings strongly suggest that those with the mutation have a worse outcome than others with familial breast cancer.

Previous studies have addressed the same question and come up with a variety of answers. However, the French group claims its study design limited the selection bias toward survival, which is common in retrospective studies.

The cohort study included 183 patients with invasive breast cancer, treated at the Institut Curie, Paris, and tested for *BRCA1* mutations. The group included 40 women with this mutation and the researchers found that overall survival was poorer for carriers (80% at 5 years) than non-carriers (91%). This is similar to findings from other large studies.

However, when analysis was limited to the 110 patients whose diagnosis-to-counselling interval was less than 36 months, the difference between the groups increased dramatically. In this cohort, overall survival was 49% among carriers compared with 85% among non-carriers. The difference in metastasis-free interval was even greater: 18% among carriers compared with 84% among carriers.

"A long time interval between breast cancer diagnosis and genetic counselling artificially increases survival time by excluding from the case group patients deceased at the time of genetic counselling," they say. The precise influence of the mutation on prognosis will be determined from prospective studies, but they conclude, "'These new data may already be taken into account when discussing the management of healthy women carriers of a *BRCA1* mutation.''

INTERVIEW

Dr Jean Pierre Armand is Director of the Federation of Cancer Societies (FECS) and a past president of the European Society of Medical Oncology (ESMO). He is a medical oncologist and Head of Medicine at the Institut Gustave-Roussy, Villejuif, France.

Dr Jean Pierre Armand

Where did you train?
Initially at Toulouse University in the south of France, and I trained in oncology in Paris. Then, at a time when we thought immunology would cure cancer, I moved to Columbia University, New York to work in immunology.

Who inspired you?
Professor PF Combes, a radiotherapist, probably never treated anyone with radiotherapy, but attracted me to oncology. Professor George Mathe convinced me I should go into oncology rather than radiotherapy, and Professor Maurice Tubiana invited me to come to the Institut Gustave-Roussy.

Why did you choose to work in the field of cancer?
It was not an early decision. I started training as an internist, but found it too broad a subject. Haematology seemed too narrow. So I explored oncology, which did not exist as a speciality at the time, as I felt it would provide me with the dimension I needed to fulfil my aspirations.

Did any other branch of medicine appeal?
Very early on, I considered psychiatry, but I am scientific by nature and dismissed it because of the lack of good methodology. I also considered specialising in infectious diseases, a field revolutionised by drugs.

Might you have done something else altogether?
I would have enjoyed ethnology. My father is a civil servant and I was born in North Africa. I learned Arabic and remain interested in exploring different cultures; especially those of the Middle East and Far East. I even went to Katmandou as part of the peace corp for 2 years.

What is your greatest regret?
I don't really have one, I could have done a lot of other things but I don't regret the career paths I didn't take. We are lucky in medicine in that we have a lot of choice. You might want to become a basic researcher or a GP, a surgeon or a psychiatrist which are totally different, but the basic medical training is the same for all of these.

If you could complete only one more task before you retire, what would it be?
To engender in young oncologists the spirit of oncology that prevailed 30 years ago. Then everyone was ready to cure cancer, but a lot of people do not seem as enthusiastic about that any more. I'm also very interested, particularly in my work with FECS, in helping to develop oncology at the European level and shaping the politics of cancer in Europe.

What is your greatest professional fear?
That in future, the patient will not be the doctor's top priority. Government authorities and pharmaceutical companies are putting a lot of pressure on us at work. I am concerned that over the coming years we will not be able to offer patients all that we would like to.

What impact has the Internet had on your working life?
I can send an e-mail to friends in oncology, in the States, China and Japan and get a reaction within a few minutes. I can discuss cases with them, ask for their feelings, raise philosophical and ethical issues. In the past, I used to wait for a visit to have such in-depth discussions. The second big advantage is access to top cancer information even from the middle of the mountains in France, miles from a big library. It is fantastic.

How do you relax?
By going with my wife and daughter to Auvergne, in central France, where I am from. Seeing year after year, the apple, pear and chestnut trees my family planted, that's very relaxing. We don't only go in the summer — if you only relax once a year you are not relaxed — but we try to go once every 3 months.

Who is your favourite author?
I don't have an exclusive favourite, but I always read Victor Hugo with great pleasure; also Alexandre Vialette, a local author, who has written a lot of clever novels. I'm enjoying the translations of Chinese and Japanese novels which have recently become available.

What do you wish you had known before you embarked on your career?
How to order priorities. As an internist, I had to handle a lot of things at the same time, which was good experience, but you have to select priorities and I learned this a little too late. You can get trapped by having too many interests; you can lose sight of your main objective.

What piece of advice would you give someone starting out now?
This probably contradicts what I've just said, but try not to specialise too early, keep an open mind and approach any type of experience with absolute involvement. Go into any project deeply and intensively. Try not to surf; it's one big danger of society today.

What is your favourite carcinogen?
I have a Chinese wife and I love Chinese food. The salt and preservatives are thought to be carcinogenic, but I don't mind. Anyway, I don't smoke.