



Newsdesk

Bring back the acetyls—a novel anticancer movement

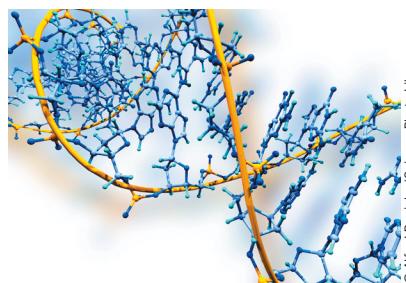
"What's done is done, and cannot be undone", says Lady Macbeth in William Shakespeare's famous Scottish play. In cancer management, this is still painfully true. Despite carcinogenesis being defined by gene mutations, mending genes remains beyond medical reach. But epigenetic researchers are now arguing that genetic damage can be undone by modifying certain histone markings. This unorthodox thinking has, in a remarkably short time, leapt from laboratory experimentation to clinical trials.

The novelty of the strategy hinges on histones—the proteins around which DNA strands are entwined. Until only recently, these globular proteins were dismissed as inert scaffolding for genetic material but it is now becoming clear that chemical species on histones can regulate the activation state of the 30 000–40 000 genes within each cell.

Histone marks are far from static. There are enzymes dedicated to either adding or cleaving acetyl, methyl, or phosphate groups to histone tails. "In some human diseases, notably cancer, it looks like many of these enzymes are messed-up and deregulated", says David Allis (University of Virginia School of Medicine, Charlottesville, VA, USA). "If you lose any of the [histone] marks, you might inappropriately activate an oncogene or silence a tumour suppressor gene. The consequences could be disastrous, [causing a cell to] develop into a cancerous state."

Mounting evidence suggests that this is indeed the case, and that unique epigenetic changes are involved in specific cancers. Paul Marks (Memorial Sloan-Kettering Cancer Center, NY, USA) has recognised that in various types of cancers there are striking defects in histone acetylation. The acetyl groups are removed by an overactive enzyme: histone deacetylase. Marks reasoned that if histone deacetylase could be deactivated then an effective anticancer strategy could be developed. "We screened over 700 different compounds that could inhibit histone deacetylase enzymes, and arrived at the structure of SAHA", says Marks of one potentially efficacious small molecule called suberoylanilide hydroxamic acid.

SAHA fits the criteria perfectly: tumour cells stop growing as acetylated groups accumulate. And in studies of experimental animals with prostate cancer, tumours were found to arrest and go into remission with little or no toxicity as a consequence of SAHA deactivation of histone deacetylase. What's more, SAHA was also found to act synergistically with either radiation or imatinib.



Epigenetic signatures offer new therapy targets.

But, however promising these laboratory results may have been, the make-or-break for any new drug is always the extent of activity seen in clinical trials. Much anticipation surrounded the phase I trials, which were set up to include patients with advanced bladder cancers or T-cell lymphomas. "These people had stopped responding to treatment and were given 3 months to live by their physicians", says Marks. At the highest doses, SAHA produced some dramatic tumour regressions, prompting phase II trials—which are currently ongoing.

SAHA is given orally and is well-tolerated. One patient has now been taking the drug for 20 months and has experienced very few side-effects. Remarkably, the disease has also stabilised. "These are wonderful results, but you have to remain [objective]", says Marks. "The field has suffered too many disappointments." Yet he has little doubt that this new compound will become a useful addition to the current range of anticancer therapeutics, and consequently, Marks has begun synthesising compounds with up to ten times the activity of SAHA.

The idea of restoring acetylation to reverse the cancer process is also being pursued by Peter Atadja's group

(Novartis Institute for Biomedical Research, East Hanover, NJ, USA). "We first had to find our own histone deacetylase inhibitors", he explains. Intensive library searches combined with iterative medicinal chemistry eventually resulted in the discovery of NVP-LAQ824, a synthetic compound that inhibits histone deacetylase and stops tumour cells from growing. Crucially, this compound was also selective. "We didn't want a compound that would kill cells [indiscriminately]. This compound can distinguish normal tissue from tumours", Atadja comments. Indeed, experiments have shown that while tumour cells apoptose, normal fibroblasts remain in cell-cycle arrest after administration of NVP-LAQ824.

When NVP-LAQ824 was tested in mice with xenograft tumours, Atadja and colleagues found that the compound not only inhibited tumour growth but also induced regression. "This is the Holy Grail of tumour treatment", says Atadja. Clinical trials to test the new compound against leukaemias and advanced solid tumours have already begun and in some patients, their cancers have substantially regressed.

Is histone acetylation the whole story? According to Atadja, the chaperone protein HSP90 also becomes acetylated following NVP-LAQ824 treatment. This may increase the overall antitumour effect because acetylation forces HSP90 to release a large number of oncoproteins.

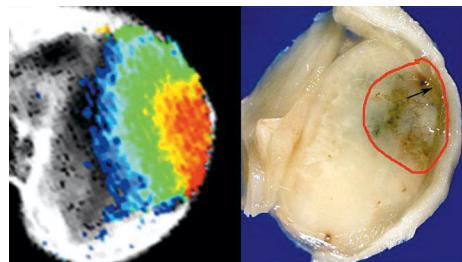
"The field is still in its infancy, yet we already have drugs at the clinical stage", commented Eric Verdin (Gladstone Institute of Virology and Immunology, University of California San Francisco, USA) at a Novartis Foundation Meeting earlier this year (May 6–9, 2003, London, UK). "Given how widely acetylation is distributed in biology, I can envisage selective inhibitors for each of the histone deacetylases and selective medical applications for each one of them." There is little doubt that we will be hearing more about histone deacetylase inhibitors very soon.

Lisa Melton

Nanoshell destruction of inoperable tumours

Material scientists are harnessing metal nanoshells—minute particles of silica covered with a thin layer of gold—for cancer therapy. The nanoparticles absorb near infrared [NIR] light, convert it to heat, and cause irreversible thermal cellular destruction (*Proc Natl Acad Sci USA* 2003; **100**: 13549–54). Plus, unlike existing thermal ablation techniques, which are limited by the amount of collateral damage to nearby normal tissue, the effects of nanoshell therapy are confined within the tumour.

Nanoshell thermal ablation combines two benign moieties—nanoshells and NIR light—in such a way that collateral damage is minimised, say Jennifer West and her colleagues at Rice University, Houston, TX, USA. West explains that the geometry of nanoshells determines what wavelength of light they absorb. “We designed nanoshells that absorbed in the NIR because there is a narrow gap in the optical spectrum where tissue is essentially transparent.” Consequently, NIR light



Nanoshell therapy induces gross pathological damage.

compared with just 10°C in tissues treated with NIR light alone. Although the experiments used intra-tumoral injections, West believes that systemic administration of nanoshells should also work because leaky blood vessels in tumours should allow for preferential accumulation.

“West and her colleagues have tailored nanoshells to be phenomenal NIR absorbers”, says Andrew Taton (University of Minnesota, Minneapolis, USA), “and this is a unique application of these objects”. However, he comments, “although tissue is technically transparent to NIR, it also scatters NIR and this will limit the depth to which nanoshells can be used for tumour ablation”. In imaging studies, counters West, “penetration depths for NIR light of up to 15 cm have been reported. However, if necessary, we could run very thin fiberoptics through catheters or laproscopic devices to get the NIR light anywhere in the body.”

Jane Bradbury

Tamoxifen-resistant cells sensitive to oestradiol

Long-term treatment with tamoxifen produces supersensitivity to oestradiol to the extent that physiological concentrations can cause apoptosis and regression of breast tumours (*J Natl Cancer Inst* 2003; **95**: 1597–1608).

Long-term tamoxifen treatment for breast cancer can result in resistance due to clonal selection of breast cancer cells that, paradoxically, start to grow in response to tamoxifen. These tumours are oestrogen-receptor- α -positive and this receptor is thought to mediate the dual actions of oestradiol on breast-cancer cells—initially as a growth stimulator and then as a growth inhibitor after long-term tamoxifen use. But, the mechanism of oestradiol-induced growth inhibition in these cells is poorly understood.

V Craig Jordan and colleagues (Robert H Lurie Comprehensive Cancer Center, Northwestern University, Chicago, USA) transplanted oestradiol-stimulated breast tumours into athymic mice, which were then treated with tamoxifen for more than 5 years to mimic a clinical situation in which long-term use of tamoxifen results in the evolution of a tamoxifen-sensitive to a tamoxifen-stimulated (and resistant) breast cancer. Groups of ten mice were randomly assigned to vehicle, tamoxifen alone, oestradiol alone, fulvestrant alone, or fulvestrant plus oestradiol. Oestradiol was given subcutaneously to achieve postmenopausal serum concentrations of 83·8 pg/mL.

In tumours whose cross-sectional area was initially 0·35 cm², oestradiol caused regression to 0·18 cm², but tamoxifen, fulvestrant, or oestradiol plus fulvestrant increased tumour growth up to 1 cm². Also, oestradiol increased the number of apoptotic cells in tumours by 23%, induced the expression of the death receptor FAS, and decreased the expression of the antiapoptotic factors HER2/NEU and NF κ B. Surprisingly, apoptosis was completely blocked in tumours treated with the combination of oestradiol plus fulvestrant.

These results “suggest that low concentrations of oestradiol are sufficient to induce apoptosis and the regression of tamoxifen-stimulated breast tumours”, say the authors, adding that “the use of fulvestrant in patients with sufficient concentrations of circulating oestrogen may exacerbate the disease by stimulating growth”. In an accompanying editorial, Daniel Hayes (University of Michigan Comprehensive Cancer Center, Ann Arbor, USA) points out that “rather than using pharmacological doses of oestrogen as first-line therapy, as was done before tamoxifen’s introduction, low doses should be used after [tamoxifen] treatment”. And he warns that “the order in which serial endocrine therapies are administered might be critical, because the combination of fulvestrant and oestrogen produced results in diametric opposition to those expected”.

Xavier Bosch

Newsdesk

Vaccine hope for acute promyelocytic leukaemia

An experimental DNA vaccine (PML-RAR α) can slow the progression of acute promyelocytic leukaemia (APL) in mice, according to new research (*Nat Med* 2003; **9**: 1413–17).

"Our findings are important because they show for the first time that a DNA vaccine directed towards an oncogene has efficacy in mice with active disease", claims lead author Rose Ann Padua (King's College Hospital, London, UK).

According to Padua, the disease in mice mimics human APL both morphologically and in its response to treatment with all transretinoic acid (ATRA), which combined with chemotherapy is the conventional treatment for patients with APL.

Padua and colleagues found that ATRA alone can induce an anti-RAR α antibody response and that DNA alone also extended survival of the mice. In combination with ATRA, the vaccine was even more effective in improving survival,

rescuing 50% of the mice from relapse and death with enduring remissions of up to a year. "This translates to half the lifespan of the animal", Padua points out.

In the immunised mice, there was also an increase in the release of interferon γ . According to Mary Disis (University of Washington, Seattle, WA, USA), these findings are quite important because the authors have targeted a biologically relevant protein in this disease and shown that active immunisation, generating an antigen-specific immune response, can improve outcome in a mouse model of APL that very closely mimics human disease.

"This model is as close as you can get to evaluating vaccine effects in human APL. Their DNA vaccine construct is one that can be readily and easily made for human use", she explains. In addition, she says, the augmentation of the protective effect of vaccination with ATRA therapy sets the stage of adding such an

approach to the standard treatment of patients with APL.

She believes that this and other studies show that the use of vaccines in cancer treatment can not only be easily intercalated into standard therapy but also the immunological effects may be increased when immunisation is given in combination with standard therapy. "Preclinical studies, such as this, set the stage for rapid introduction of combination biological therapies to the clinic", Disis comments.

The next step, Padua says, is to elucidate the mechanism of action to improve the treatment further. "We plan to conduct clinical trials in relapsed APL patients. Immunotherapy is well tolerated and quality of life using such a treatment strategy makes this an attractive option. The proof of principle will enable us to develop vaccines against other fusion genes, which are found in 50% of acute leukaemia", she concludes.

Khabir Ahmad

Phase I melanoma trial puts Chile on the map

A Chilean phase I trial with an autologous dendritic cell (DC) vaccine against malignant melanoma has shown the agent to be safe and capable of producing an antitumour immune response. Although similar trials are taking place in the USA (*Proc Am Soc Clin Oncol* 2003; **22**: 178, *J Clin Oncol* 2003; **21**: 4016–26), this is the first immunotherapy study in Chile. The project is being carried out at the University of Chile, Santiago, with support from the Karolinska Institute, Stockholm, Sweden.

Since 2000, 13 patients with stage IV melanoma have been enrolled in the trial. Researchers used leukapheresis to extract peripheral blood and then treated the cells with interleukin 4 and granulocyte-macrophage-stimulating factor to obtain DCs, which were then incubated with a lysate of three allogenic melanoma cell lines and tumour necrosis factor α before being injected back into the patients in four



New immunology laboratory in Santiago, Chile.

doses over 2 months. No serious toxicity has been detected so far. Although there has been no effect on melanoma progression, analyses have shown the peripheral mononuclear cells of eight patients (62%) produced increased interferon γ in response to allogenic melanoma cells, and six patients (46%) responded positively to delayed-type hypersensitivity tests.

On the basis of these results the researchers were granted state funding to build a laboratory that complied

with international standards. It is the first cancer-cell immunotherapy centre in South America. The team are now starting a phase II trial of a regimen that intersperses the vaccine with low doses of interleukin 2. "Interleukin 2 stimulates the propagation of cytotoxic T-lymphocytes in vivo. We are using low doses because it is possible to obtain the same effect as with high doses but without the side-effects", says Flavio Salazar, BioMedical Sciences Institute, University of Chile, Santiago.

Mario Rosemblatt, Life Science Foundation, Santiago, Chile, applauds the initiative: "It is admirable that there are people prepared to use their knowledge of basic research for the benefit of Chilean patients. This project is very important because, despite having the necessary capability, very few people are conducting pioneering medicine in Chile".

Claudia Orellana

Vital gene linked to parathyroid carcinoma

Researchers in the USA have reported a link between apparently sporadic parathyroid carcinomas and somatic germline *HRPT2* mutations, opening the way for better diagnostic strategies and novel treatments. "HRPT2 mutation certainly seems to be fundamental to parathyroid carcinoma, not just a 'marker' of the malignant process", comments lead author Andrew Arnold (Center for Molecular Medicine, University of Connecticut School of Medicine, Farmington, CT, USA).

Parathyroid carcinoma, a rare cause of primary hyperparathyroidism, is treated successfully by surgery in only 30% of patients and recurrence and distant metastases cause relentless hypercalcaemia, severe metabolic disruption, and death.

In the current study, investigators sequenced the *HRPT2* gene in parathyroid carcinomas from 15 patients with no known family history of primary hyperparathyroidism. Tumours from ten patients had *HTPR2* mutations, and hence predicted to have inactivated parafibromin protein. Mutations were somatic in seven patients but surprisingly, three patients were found to have germ-line mutations. (*New Engl J Med* 2003; **349**: 1722–28).

"Our demonstration that many parathyroid carcinomas had somatic *HRPT2* mutations indicates that such mutations confer an important selective advantage when they occur in a parathyroid cell, and place that cell's descendants on the road to malignancy", says Arnold. Henry Kronenberg (Massachusetts General Hospital, Boston, NY, USA) views the observation that the *HRPT2* gene is mutated in most parathyroid cancers as a very important advance. "Like many endocrine tissues, parathyroid cells, even when neoplastic, are almost never malignant", he explains, and adds that if the normal function of this gene is understood, ways of reversing the malignant state of parathyroid cells could be developed. Co-author Catherine Larsson (Karolinska Hospital, Stockholm, Sweden) agrees it is likely that restoring the malignant cell's deficient parafibromin function could have an important antitumour effect. "This would be a tremendous

advance for patients with metastatic disease, who are beyond the stage where surgical cure is possible", she says.

Kronenberg says that normal tissue must be now checked for the gene in patients with *HRPT2* mutations. "Individuals in these families who are identified as being at risk can then be monitored on a regular basis—simple blood tests for serum calcium to detect the tumour at an early stage will offer

excellent chances for prevention or cure of the cancer before metastatic spread. Such increased awareness and testing is likely to save many lives", predicts Arnold. "There might even be a time when parathyroid lesions are aspirated for genomic analysis and checked for *HRPT2* somatic mutations but that will require several advances in genomic technology", adds Kronenberg.

Kathryn Senior

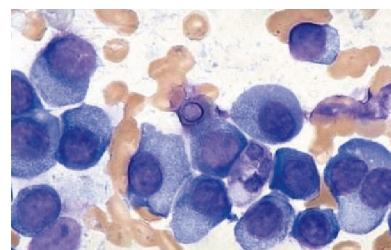
Australia approves thalidomide

Australia has become the first country to approve thalidomide—the drug that caused a spate of birth defects in the 1950s and early 1960s—for the treatment of multiple myeloma after failure of standard therapies, allowing its use to be tightly regulated. The decision to approve thalidomide for multiple myeloma has been overdue, says Bart Barlogie (Arkansas Cancer Research Center, Little Rock, AR, USA).

Since thalidomide was withdrawn from world-markets in 1961, the drug has gradually returned to practice in a range of diseases, including leprosy, AIDS, graft-versus-host disease, and various cancers. But in 1998, under pressure to stop the black-market use of the drug, the FDA approved thalidomide for the treatment of erythema nodosum leprosum (ENL)—the only condition at the time where enough data were available to prove the efficacy of thalidomide.

However, a few months earlier, Barlogie had tried the drug in patients with refractory multiple myeloma and discovered that some people recovered. The news spread like wildfire around the world, and soon oncologists in other countries confirmed Barlogie's finding that thalidomide causes 50% reduction in tumour burden in about a third of patients with refractory disease. Thalidomide is now being considered for first-line management of the disease and for maintenance therapy. "It is the best treatment advance in the past 25 years, and people are doing well with it", says Gareth Morgan, Chair of the UK Myeloma Forum Scientific Subcommittee.

To date, over 100 000 patients worldwide have received thalidomide, a large proportion of those being myeloma patients. But apart from the USA, where oncologists can prescribe the drug off-label, use of thalidomide has been unregulated. The pharmaceutical company Pharmion (Boulder, CO, USA) last year filed applications with Australia's Therapeutic Goods



TGA approves thalidomide for myeloma.

Administration (TGA) and with the European Agency for the Evaluation of Medicinal Products (EMEA), seeking approval of thalidomide for the treatment of multiple myeloma and ENL in conjunction with a rigorous risk management programme. The company received a positive decision from the TGA in October this year.

"I think they wanted a high-quality, tightly controlled product as soon as possible," says Steve Slack, General Manager of Pharmion. The decision in Europe is still outstanding and it may be a particularly tough one, as most of the birth defect cases occurred in Germany and the UK. A strict risk management programme is therefore an integral part of this license application as well.

Martina Habeck

Newsdesk

Cone-snail depletion threatens medical research

The loss of marine snails from the Tropics could have devastating effects on the development of new cancer drugs, say scientists. Cone snails, prized by collectors, are a potentially rich source of powerful new medicines. But wild populations are being decimated by overfishing and by destruction of the coral reefs and mangroves they inhabit, says Eric Chivian (Harvard Medical School, Boston, MA, USA) and colleagues (*Science* 2003; **302**: 391).

About 500 species of cone snails are known, each producing a unique combination of toxins with which they paralyse their prey. Only about 100 of an estimated 50 000 conotoxins have been characterised so far, and only a few tested for pharmacological activity. "We will never know what drugs we might have discovered from species that have gone extinct", says co-author Callum Roberts (University of York, UK). "The risk of extinction is greatest for species with a narrow geographical distribution, and one in five cone snails are in this category. Their marine habitats are disappearing as fast as the rainforests on land." John Reynolds (University of East Anglia, Norwich, UK) comments: "Cone snails are particularly vulnerable, because they live in shallow water, where even the rarer ones are fairly easy to collect."

Conotoxins act on various receptors to block neural transmission at the neuromuscular junction. One of the attractions for researchers is their small size (10–30 aminoacids), which makes synthetic derivatives easy to manufacture. They are also very stable and selective in their receptor binding sites.

Intrathecal ziconotide, a synthetic conotoxin that blocks a voltage-gated calcium channel in nerve terminals, is in phase III clinical trials for the relief of intractable pain, eg, in patients with cancer or AIDS. The data show that ziconotide is 1000 times more potent than morphine. Researchers at the University of Utah (Salt Lake City, UT, USA), who are beginning clinical trials for pain treatment with another cone-snail-derived peptide, are also building up a DNA library of natural conotoxins.



Cone snails need protecting.

small-cell lung cancer, a tumour of neuroectodermal origin that expresses voltage-gated calcium channel proteins.

Chivian and colleagues suggest that cone snails should be listed under the Convention on International Trade in Endangered Species, which would require trading countries to develop management plans to ensure that collection from the wild is sustainable. "Efforts to cultivate cone snails have so far failed", says Roberts. "A surer way to sustain supplies is to invest in protecting wild stocks and their habitats. We urge companies seeking benefit from cone snail peptides to support this effort."

Dorothy Bonn

Formaldehyde link to cancer

Investigators carrying out the largest extended follow-up of industrial workers to date have reported an increased risk of death from leukaemia (particularly myeloid leukaemia) in individuals exposed to formaldehyde. (*J Natl Cancer Inst* 2003; **95**: 1615–23).

Researchers compared mortality in 25 619 workers (producing formaldehyde, molded plastics, photographic film, and plywood) exposed to varying amounts of formaldehyde, from background concentrations of 0·1 ppm to high short-term exposures of more than 4·0 ppm. The average exposure was associated with an increase in lymphohaematopoietic cancers.

"But the most interesting and extraordinary measure was peak exposure, which has not been studied in an industrial cohort of formaldehyde workers before", says lead author Michael Hauptmann (National Cancer Institute, Bethesda, MD, USA). Peak exposure defined workers whose average exposure was exceeded by short bursts of high contact with formaldehyde, for example, when loading mixing machines. Workers with peak exposures >4·0 ppm had a relative risk of 3·5 of myeloid leukaemia.

However, another study published in the same issue of *J Natl Cancer Inst*

(2003; **95**: 1608–15) followed 14 014 British factory workers who produced or used formaldehyde and found a positive association with risk of lung cancer. Overall, the cohort showed no evidence of haematopoietic cancers.

Lead author David Coggon (Medical Research Council Environmental Epidemiology Unit, Southampton, UK) categorised workers into four exposure categories with high exposure more than 2 ppm. "However, the factory with greatest exposures was located where lung cancer rates are higher than average", explains Coggon. When adjusted for location, the excess was less but still significant.

"These studies present different conclusions about leukaemia risk among formaldehyde workers", comments James J Collins (Dow Chemical Company, MI, USA). "Because of the biological implausibility of this finding and the inconsistency across studies, formaldehyde is probably not a leukaemogen", he states. "However, increased risk of leukaemia and other diseases such as pancreatic cancer have been observed among pathologists and may be due to better diagnosis or to occupational exposures other than formaldehyde in this profession."

Kathleen Nelson

Chemoprevention: eat ginger, rub on pomegranate

Eating ginger and rubbing on pomegranate extract could prevent certain cancers, suggest two studies presented at the Annual International Conference on Frontiers in Cancer Prevention Research, Phoenix, Arizona, USA (26–30 October, 2003).

In Asian medicine, ginger is used to treat a wide range of conditions and modern enthusiasts claim it is also an antiemetic, an antirheumatic, and a preventative of cardiovascular disease. Now, Ann Bode and Zigang Dong of the University of Minnesota, Minneapolis, USA, provide evidence that it might also prevent cancer.

Bode and co-workers fed athymic nude mice with 500 mg of [6]-gingerol, or a placebo, three times per week for 2 weeks before injecting human colon-cancer cells. Feeding with [6]-gingerol, or the placebo, then continued. The results showed that tumours in the treated mice took longer to appear and grow, and were possibly less invasive than those in the controls.

"The mechanism is still to be determined", says Bode. "However,

[6]-gingerol may inhibit tumour growth by inhibiting AP1 activation or inducing tumour-cell death."

In another presentation, researchers at the University of Wisconsin, Madison, USA, reported that rubbing pomegranate extract on the skin might protect against skin tumours. Pome-



Pomegranate extract may prevent skin cancer.

Applying 2 mg of pomegranate extract on the skin of mice before exposing them to a carcinogenic agent, inhibited the appearance of erythema and hyperplasia, and the activity of epithelial ornithine decarboxylase. It also inhibited MAPK-associated tumour-promoting pathways and activated NFkB activity (a natural tumour suppressor). Furthermore, at 16 weeks, tumour incidence in the control mice was more than three times higher than that of the pomegranate-treated mice.

"For the first time we have clear evidence that pomegranate extract possesses anti-skin-tumour effects", says study leader Farrukh Afaq. "With such a variety of pathways inhibited, we are confident of its therapeutic value."

However, Manel Esteller (Spanish National Cancer Centre, Madrid, Spain) warns: "Many compounds have failed to meet expectations, such as the retinoids in the prevention of lung cancer. These new agents must now pass rigorous epidemiological studies [before we can be sure of their utility]."

Adrian Burton

and testing for *BRCA1* and *BRCA2* (for hereditary breast and ovarian cancer); *hMSH2* and *hMLH1* (for hereditary non-polyposis colorectal cancer); and *Ret* (for multiple endocrine neoplasia types 2A and 2B, and familial medullary thyroid cancer).

The location of the registry in southern India is also an important aspect because arranged marriages between cousins is highly prevalent in this part of the country—increasing the risk of certain hereditary cancers. "The risk for hereditary cancers among an inbred population is likely to be high. One of the families with breast cancer analysed recently, was found to have a uncle-niece parentage and carried a deleterious two-base novel deletion in the *BRCA1* gene. So, it is critical to study these populations for mutations in the relevant genes", concludes Rajkumar.

Dinesh C Sharma

Indian registry to study hereditary cancers

Mathematical models used by developed countries to predict cancer risk have limited applicability in India because of differences in disease incidence. In a move to eliminate this problem, India has established the Population-based Hereditary Cancer Registry at the Cancer Institute in Chennai. Despite 14 other population-based registries in the country, this registry will collate, for the first time, data on the incidence of hereditary cancers.

The new registry covers the Chennai metropolitan area and data is being obtained from government hospitals and private nursing homes. Data collection is being done by trained social investigators using a questionnaire-based approach. In addition, the registry will be linked to the Madras Metropolitan Tumour Registry that records the incidence of all cancers in the city of Chennai, India.

The occurrence of hereditary cancers, such as breast and ovarian carcinoma and non-polyposis colorectal cancer have been reported before in Indian populations. However, the new registry—coupled with data from genomic sequencing—will help researchers do linkage analysis to ascertain the inter-relation between specific genes and specific cancers and hence design appropriate preventative measures for people who are carriers of mutated genes. So far, about 190 cases have been registered. "It is too early for us to talk about linkages but the mutation analysis is continuing and we hope to be able to address this issue once we complete the analysis", says Thangarajan Rajkumar (Cancer Institute, Chennai, India).

The institute has already generated some initial data about hereditary cancers. The clinic has started to offer high-risk families genetic counselling

Newsdesk

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Risk of breast-conserving surgery

Young women who opt for breast-conserving surgery as treatment for breast cancer have a higher risk of recurrence than those who have a mastectomy (*Ann Oncol* 2003; **14**: 1617–22). Researchers compared 88 patients who had a lumpectomy plus radiotherapy with 91 women who had a mastectomy. The risk of recurrence was five times less in women who had lumpectomy in the first 5 years after surgery but then increased to 12 times more after 5 years. The investigators also reported that late recurrence was more common in women under 40 years who had breast-conserving surgery. There was no difference in survival or incidence of metastasis.

Antismoking campaign success

An 8-year smoking cessation study carried out in 17 states in the USA has reported a reduction in the prevalence of adult smoking (*J Natl Cancer Inst* 2003; **95**: 1681–91). The American Stop Smoking Intervention Study (ASSIST), set up by the National Cancer Institute in 1991 gave funding to encourage smoke-free environments, to limit access to and availability of tobacco, to promote antismoking advertising, and increase taxes on tobacco. States given funding achieved a greater reduction in the prevalence of adult smoking and had a lower per capita cigarette consumption than states not involved in the study. The authors estimate that a nationwide implementation of the ASSIST programme would result in 278 700 fewer smokers.



Glioma gene blocked

Antisense oligonucleotide strands have been used successfully to block a gene involved in the progression and recurrence of glioma (*Mol Cancer Ther* 2003; **2**: 985–94). Highly specific antisense oligonucleotides against the laminin-8 gene were tested in vitro using human glioblastoma multiforme cells co-cultured with normal human brain microvascular endothelial cells. The oligonucleotides blocked the synthesis of laminin-8 protein, which has been shown to be involved in the development of new tumour blood vessels. Furthermore, the antisense strands were able to block cellular invasion through matrigel leaving the authors to conclude that as well as aiding growth of tumour vasculature, laminin 8 may also directly increase the invasive potential of the cells.

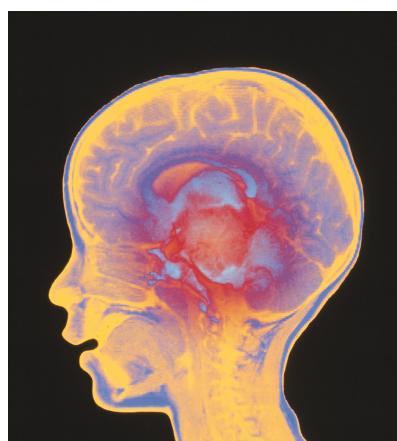
Mesothelioma marker identified

A new blood test to detect mesothelioma could potentially be used to monitor individuals at risk from the disease, such as people exposed to asbestos (*Lancet* 2003; **362**: 1612–16). The test identifies soluble mesothelin-related proteins (SMR), which are released by mesothelial cells into the bloodstream. The researchers reported that 84% of 44 patients with mesothelioma had high concentrations of SMR compared with 2% of 160 patients who had other inflammatory or malignant lung and pleural diseases. Furthermore, in general, increases in concentrations of SMR were associated with the extent of tumour bulk. The authors believe the test could be a useful tool for diagnosis and monitoring disease progression.

Circadian rhythms

The growth of tumour cells is controlled by a gene clock, say researchers at the International Conference on Molecular Targets and Cancer Therapeutics (Nov 17–21, 2003, Boston, MA, USA). Eight clock genes are thought to regulate normal cells but it is not known whether tumour cells also follow circadian patterns. 30 mice were injected with neoplastic cells and subjected to a cycle of 12 h in the dark and 12 h in the light. Tumours grew

about twice as quickly in the light phase than in the dark phase, and the tumour mitotic index was higher in the light phase. The researchers believe that genes regulating the circadian clock may offer potential targets for novel cancer treatments.



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Skin disorder link to lymphoma

Patients with psoriasis have a three times higher risk of developing lymphoma than people without the skin disorder (*Arch Dermatol* 2003; **139**: 1425–29). Researchers analysed a random sample of patients over the age of 65 registered with a family doctor in the UK. 2718 patients had psoriasis compared with 105 203 patients without the disease. Patients with psoriasis had an extra 122 lymphomas per 100 000 patients annually. It is not yet known whether the increased rate of lymphoma in this group was associated with either the severity of the disease or the treatment given.

Brachytherapy popular in USA

The percentage of men in the USA with clinically localised prostate cancer who were treated with brachytherapy has increased dramatically (*Cancer* 2003; **98**: 1987–94). In 1994, less than 5% of patients were treated with brachytherapy compared with 36% of patients in 1999. However, half of patients treated with brachytherapy also received conventional external-beam radiation. Patients treated with brachytherapy tended to be younger, have lower PSA concentrations, and have a more favourable prognosis.