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First reading of EU's animal research report

Amendments to the EU Directive on the protection of animals used for scientific purposes (Review of Directive 86/609/EEC) were passed by the Agriculture Committee on 31st March, 2009. Some aspects of the original draft were watered down by MEPs in response to concerns raised by the medical research community. The plenary vote on the amended Directive is timetabled for May 4–7, 2009.

The amendments were drafted by MEP Neil Parish (UK) with the aim of reducing the number of animals used for scientific research to a minimum in the EU, and subjecting planned tests to compulsory ethical assessment 'to take account of the public's concerns.'

MEPs endorsed the proposed ban on the use of great apes threatened with extinction, except for experiments intended to conserve these species. However they rejected aspects of the proposal which would drastically restrict the use of primates such as ouistitis and macaques and 'could penalise European research to the advantage of its American or Asian competitors'.

ECCO – the European CanCer Organisation – had raised particular concerns about amendment 311 which called for all applications for research projects involving animals to be subject to public consultation in order that regulatory authorities may have 'access to the widest range of views on which to base decisions.'

President Professor Alexander Eggermont wrote to all members of the Agriculture Committee in advance of the vote. He said that while the proposal may seem to bring about an increase in transparency 'medical researchers know from experience that the vast majority of views transmitted will come through organised write-in campaigns from animal rights groups, and collecting and collating them all will add months to the already lengthy process of authorisation.

'On behalf of European patients, doctors, and researchers, we ask you most sincerely to allow us to continue to work to reduce the burden of cancer and not to put unnecessary barriers in our way.'

Amendment 311 was dropped by MEPs and Ms Ingrid van den Neucker, ECCO's Public Affairs Manager said the debate had been 'generally positive'. Concerns remain, however, about amendments which were passed, such as the data-sharing requirement for laboratories, and the obligation for animal research facilities to be staffed 24 hours a day, which would – if the amendments are passed – increase the costs of research.

Chemoprevention in prostate cancer

US men taking annual prostate-specific antigen (PSA) tests are being advised to discuss with their clinician the pros and cons of taking a 5α-reductase inhibitor, according to new guidelines.

The American Society of Clinical Oncology (ASCO) and the American Urological Society (AUA) have produced a joint guideline on chemoprevention in prostate cancer. It applies to men who show no signs of prostate cancer, have a PSA score of 3.0 or below and who already take an annual PSA test, or expect to.

The advantages of taking a 5α-reductase inhibitor such as finasteride, according to ASCO, are a lower risk of prostate cancer, improvement in urinary problems (if present), and the reduction of future urinary problems. Potential risks include the possibility of developing high-grade prostate cancer and sexual problems lasting one to two years.

The recommendation is based on clinical trials in which men took a 5α-reductase inhibitor for between 1 and 7 years. In the largest trial, the Prostate Cancer Prevention Trial (PCPT), finasteride lowered the risk of developing the disease: of 1000 men taking the drug for 7 years, 15 fewer men got prostate cancer, compared to controls. However, in this treatment group, there were 3 more cases of high-grade prostate cancer, compared to those not taking the drug.

The ASCO guidelines state that more recent studies suggest the drugs 'do not actually increase the risk of developing high-grade prostate cancer, but rather increase the ability of the PSA test to find high-grade cancers that are already there.'

The guideline only applies to men who are receiving regular screening for prostate cancer.

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Optimising outcomes in RCC

Treatment of metastatic renal cell cancer (mRCC) is moving into an era of targeted rather than cytokine therapy, oncologists and urologists attending the European Association of Urology (EAU) meeting were told (Stockholm, Sweden 17-21 March, 2009). Latest EAU guidelines say sunitinib malate (Sutent) should now be first-line therapy with interferon-alpha (IFN-a) used only in combination with bevacizumab (Avastin).

Final data from a phase III trial of sunitinib vs IFN-a, presented at EAU, confirm that sunitinib achieved a median overall survival of 28 months compared to 14 months for IFN-a only. At a Pfizer-sponsored symposium, Professor Martin Gore (Imperial College, London), said ensuring optimal dose and duration of sunitinib maximises outcomes. Patients followed for 6 months showed a 31% response rate but by 11 months the response rate was 39%. 'The higher the amount of drug the patient is exposed to the more likely their tumours will respond,' he explained. 'This doesn't mean pushing up doses but seeing they receive an effective dose for sufficient time.'

The recommended dose is one 50mg tablet daily taken orally in a 6-week cycle consisting of 4 weeks on treatment followed by a 2-week break. Patients remain on treatment 10 to 12 months on average. Where dosage is reduced in anticipation, or because of, side effects, patients may not derive benefit, he warned. The same applied to stopping treatment prematurely or interrupting it for extended periods. Basic research shows sunitinib's anti-angiogenic benefits are likely to reverse quickly, he added.

Pre-treating patients at risk of side effects may reduce the need to lower dosage or interrupt treatment. And patients with concerns should have continuous access to a clinician or specialist nurse, he emphasised. 'It's not good enough to give them a leaflet, or even to go through a leaflet with them. They need repeated education.'

Olwen Glynn Owen attended EAU with support from Pfizer

HIV therapy: a revolutionary new direction?

Doctors in Germany have successful controlled HIV (human immunodeficiency virus) infection in a patient who also had acute myeloid leukaemia. They transplanted bone marrow cells from an HIV-resistant donor: an approach now thought to have implications for the future treatment of HIV (*N Engl J Med* 2009; 360: 692–8).

Professor Eckhard Thiel (Charité University Hospital, Berlin, Germany), one of the authors of the NEJM paper, presented the results at the 35th Annual Meeting of the European Group for Blood and Marrow Transplantation (Göteborg, Sweden, 29 March – 1 April, 2009). He said transplantation of stem cells from people who are naturally resistant to HIV 'could offer a new direction in HIV research and therapy'.

In order to infect human cells, HIV interacts with both the CD4 receptor, and another, usually the CCR5 receptor. Approximately 1–3% people do not express these CCR5 receptors because of a genetic abnormality, a homozygous CCr5 delta32 deletion. These people are naturally highly resistant to HIV infection because the virus cannot enter their cells.

The 40 year old man had acute myeloid leukaemia which was not controlled by chemotherapy. He received 2 bone marrow stem cell transplants from a donor (who had been deliberately screened for the CCr5 HIV resistant gene).

After follow up of 2 years, the patient is still free of the cancer and – remarkably – the HIV infection. No trace of the virus has been found in blood, gut or brain. His blood and marrow cells have converted to the CCr5-free, HIV-resistant type and CD4 T cells, normally destroyed by HIV, have returned to normal levels. He has not received HIV therapy since his first transplant.

Professor Thiel said that the 'groundbreaking' case should encourage further research into new treatments that target the CCR5 receptor to make people resistant to HIV.

Paradox of anti-angiogenic drugs

Angiogenesis inhibitors may promote rather than block cancer growth when given at low doses, say UK researchers. The finding may help explain why successful treatments sometimes fail (*Nature Medicine March* 2009).

Using an unlicensed drug called cilengitide, the team at the Institute of Cancer, London, UK, showed that angiogenesis inhibitors which target integrins can alter the way in which integrins and VEGF receptors move inside blood vessels. Low doses of the drug actually promoted cell movement and angiogenesis, while higher concentrations had the opposite effect.

'Our study revealed a previously unknown mechanism through which drugs such as cilengitide behave,' said lead author Dr. Andy Reynolds. 'These results may explain why initial results from early stage clinical trials have not been as promising as hoped.

'Knowledge of this mechanism will help us develop new ways to make these drugs as effective as possible. In the future, we may be able to combine these inhibitors with other drugs to maximise their effectiveness for patients.'

The study coincides with the publication of other research, showing that angiogenesis inhibitors such as sunitinib (Sutent) can sometimes encourage tumour growth rather than stunt it (Cancer Cell doi: 10.1016/j.ccr.2009.01.021; and 10.1016/j.ccr.2009.01.027). It is possible the cilengitide findings might help to explain why this can happen, though the study did not seek to do so.

Dr. Lesley Walker, Cancer Research UK, said it could be that similar mechanisms could explain why sunitinib and bevacizumab (Avastin) can sometimes fail. 'Drugs redirect the body's complex signalling systems. Sometimes very subtle alterations to the way a drug is administered, or subtle changes to a drug's structure, can have a huge impact on its effectiveness,' she said.

EUROFILE

Partnership aims to turn cancer plans into reality

The European Commission has made significant progress on a cancer action plan it began working on in 2008 with the political backing of Europe's health ministers (see *EJC News* 2008:44). The plan addresses inequalities in cancer prevention and control around Europe, focusing on primary prevention, best practice and research co-ordination. The Commission is set to present it to EU governments and the European Parliament for approval by July 2009.

With virtually no new funding available, the Commission will create a specific partnership of stakeholders to work with existing resources – including unclaimed structural funds – and use its political leverage to help countries overcome obstacles in their national cancer plans.

Partners will include national authorities, regulatory bodies, health care professionals, patient groups, civil society, the research community, the pharmaceutical industry, health insurers, and academia. The tobacco industry will be excluded, and possibly also the drinks industry.

'What we are trying to do here is a bit experimental,' says Nick Fahy, head of the health information unit in the Commission directorate for health and consumers. 'It's not the normal approach at EU level. It's not legislation. It's not Brussels telling member states what to do. It's trying to use the enormous energy that exists in the area of cancer to bring stakeholders together, to really work together in turning national cancer plans into reality, and bring about real change.'

Tackling the problems faced in establishing population based screening programmes will be one of the main priorities. The Commission will fund a pilot EU-wide accreditation scheme for breast cancer screening, diagnosis and management. The scheme is expected to be run by the International Agency for Research on Cancer (IARC) in collaboration with the European Cooperation for Accreditation (EA), a group of government-mandated accreditation organisations across Europe. The Commission envisages a voluntary scheme that countries can opt into. If successful, it would lead to accreditation schemes for cervical and colorectal cancer.

However the bulk of funding for implementing national changes will have to be found elsewhere. The Commission is keen for member states to make better use of EU structural funds – the budget the EU provides for developing national infrastructure. The current fund set for the period running from 2007 to 2013, is some 277 billion euros.

'THE EU'S STRUCTURAL FUNDS CAN BE USED FOR TRAINING AND PREVENTION PROGRAMMES. BUT PEOPLE ARE NOT APPLYING'

'Member states have the possibility to use structural funds for health infrastructure. It can mean building hospitals, but it can also mean human infrastructure, such as training, prevention programmes – all sorts of things. But not much use has been made of it so far,' explains Fahy.

The partnership will help countries get their hands on the money. 'The funds are available, the legal framework is there, so what we now need to work out is how concretely we can make this happen and bring together the different expertise. Maybe it's that the right people aren't sat in a room together, talking to each other about how to put together a bid for structural fund money that would actually help to improve cancer care,' says Fahy.

Another main priority of the partnership will be tackling the duplication of research across Europe and identifying any gaps. The mainstay of cancer research in Europe is conducted at national level with a mix of public and private funding. 'In bringing together all the different partners involved in financing cancer research across Europe, at least we'll know what everyone else is financing,' says Fahy.

Some research priorities have already been identified by stakeholders in the course of consultations with the Commission. '[These are] broader areas, rather than pure clinical research,' says Fahy. 'In particular, models of care – how can we better understand precisely how we go about providing good quality integrated cancer care.'

Although no new funding is likely to be available until 2013 for any research priorities identified by the partnership, the Commission believes that collaborative projects could still be launched. 'We can refocus some of the funding which already exists, and use the health programme to provide scientific support and help facilitate the whole process,' says Fahy. Structural funds could also be used to conduct this research.

The partnership plan has been well received by stakeholders. The Association of European Cancer Leagues (ECL) feels it could mobilise governments if well composed. 'The partnership needs to have a mechanism for ensuring a balanced, qualified representation among stakeholders. It would be important that national representatives do not participate as observers, but as active participants willing to table commitments,' says ECL director Wendy Tse Yared. This has not happened in the past, she warns. 'The partnership needs to learn from experiences of the alcohol forum and nutrition platform - similar previous mechanisms.'

According to Andreas Ullrich, medical officer for cancer alliances at the World Health Organisation, 'The partnership is a great opportunity for action on national cancer plans. We want European countries to have plans which are comprehensive. They all vary. And we want them all to take action,' he says.

The European Cancer Patient Coalition proposes that the Commission produce a list of basic principles on what should be included in national cancer plans, as part of its coordinating role. 'This would include some indication of a budget for the implementation of the plan,' says Hildrun Sundseth, head of EU Policy at the ECPC. 'If there's no budget included then it's just a nice but meaningless document.'

Saffina Rana
Brussels

Cancer vaccines: breakthrough imminent?

Prostate cancer may soon become one of the first cancers for which a vaccine will be standard treatment, Professor Angus Dalgleish (St. George's Hospital, London, UK) told the UK's Institute of Clinical Research 30th Anniversary Conference (Birmingham, UK; March 17–18, 2009).

Sipuleucel-T (Dendreon's Provenge), consisting of autologous dendritic cells complexed with the prostatic acid phosphatase (PAP) antigen and granulocyte macrophage-colony stimulating factor (GM-CSF), is in late-stage development for the treatment of metastatic, androgen-independent prostate cancer. Infusion of sipuleucel-T into a patient can stimulate a T cell response against prostate cancer cells.

Two studies initially failed to meet the required primary endpoints but an increased survival in the vaccine arms led to FDA consideration. However, Dendreon recently claimed that sipuleucel-T is close to reaching its target hazard ratio and a statistically significant survival benefit.

The results, together with a favourable safety profile, suggest that sipuleucel-T could become the first true cellular immunotherapy on the market. But GVAX (Cell Genesys) and Onyvax-P (Onyvax) are also currently involved in late-stage trials.

Prostate cancer is not the only field likely to benefit from vaccines. Promising late-stage trials on lung cancer vaccines are also ongoing, involving ASCI (GlaxoSmithKline), Stimuvax (Bio mira Merck KGaA) and Lucanix (NovaRx).

These developments provide welcome relief after recent disappointments in several melanoma vaccine trials, notably the discontinuation of the Canvaxin (CancerVax) phase III trials for both stage III and IV melanoma due to the lack of any overall survival benefit and the suggestion of possible harm (*EJC News* 2008:16).

Problems with melanoma vaccines could be overcome: 'We can improve the background by getting the modality sequence right and by getting the treatment started with vaccines as early as possible,' Professor Dalgleish said. 'All future melanoma vaccine studies are doomed to failure unless you can select correct patients who will benefit.'

Future success will lie in choosing the right disease, stage and combination with other modalities, and in getting the modality sequence right, he said: 'Patients who are going to survive beyond a year are those who are going to benefit from vaccines.'

Robert Day-Webb

'Rigorous approach needed' to find preventive agents

Carefully-designed trials are needed to find novel chemopreventive agents derived from normal diets, Professor Will Steward (University of Leicester, UK) told the meeting. He and his team have taken several novel polyphenolic compounds derived from dietary constituents into clinical trials.

'We will find things if we do the right trials,' said Professor Steward. 'The trouble is, the trials that have been done so far have been dreadful and badly designed. We need proper trials and hopefully that's what we'll move to with a lot more thought now.'

Professor Will Stewart

Professor Steward's team are rigorously investigating several compounds identified in epidemiological research. So far, they have taken curcumin, resveratrol (derived from grapes and several other fruits) and extracts of green and black tea into human studies.

Curcumin, a polyphenol from turmeric is about to enter a Cancer Research UK funded pilot study with a view to going into a large randomised prevention study. Turmeric has been used for thousands of years for food preservation, flavouring and colouring, and the Asian diet typically consists of 1.5 g per day. Turmeric has also been used widely in Asia as an anti-inflammatory treatment, for neoplasia and for wound healing.

More recently, curcumin was identified as being responsible for most of the biological effects of turmeric, and epidemiological data has suggested that curcumin has chemopreventive potential.

To date, chemoprevention has been shown to significantly reduce the incidence of breast and prostate cancer, and current trials are focusing on reducing colorectal and head and neck cancer incidence, he said.

R D-W

A future of financial headaches?

Increasing numbers of treatments are likely to be restricted in future either to subgroups of patients most likely to benefit or those with the most comprehensive health insurance, according to Professor Nicholas James (University of Birmingham, Birmingham, UK).

'This clearly represents a huge political problem which I feel has been largely neglected by politicians to date,' said Professor James.

For surgery and radiotherapy, the cost benefit ratio is such that the ideal of universal coverage, at least in Western economies, is potentially achievable, he said but for expensive new drugs 'it is becoming increasingly difficult to deliver universal access even in the richest Western economies and the gap between what is provided and what could be provided is widening.'

Professor James believes that, despite obvious differences in health care systems across the globe, the underlying problem is the same. He foresees a major clash of cultures for all major Western health care systems inflamed by a rapid inflation of drug costs (with new product licences and migration from end-stage to adjuvant stage disease) and squeezed public finance budgets.

R D-W

PODIUM

What Darwin can tell us about cancer

Professor Richard Sullivan (London School of Economics and Political Science, UK & South East London Integrated Cancer Centre, London) is co-chair of the European Cancer Research Managers (ECRM) Foundation. He has an interest in Darwinian Medicine and talks to EJC in 2009, the bicentenary year of the birth of Charles Darwin and the 150th anniversary of the publication of the Origin of Species.

Is evolution relevant in cancer?
Darwinian medicine, a term pioneered by Randy Nesse, gives us a new way of thinking about the evolution of cancer. Generally, in medicine, we are concerned about the immediate, proximate problem – the disease – and we never ask why things are the way they are. We consider cancer a disease, and cancer-causing genes 'broken', but Darwinian medicine invites us to think in terms of phenotypic variation, selection, genetic drift, inheritance and evolutionary pressures such as predation as explained by Prof Mel Greaves (ICR, London) in his wonderful book *Cancer: the Evolutionary Legacy.*

It's not immediately obvious why Darwin should be important for cancer - childhood cancers occur too infrequently for sexual selection to have any meaningful impact, and most adult cancers appear once individuals are past their reproductive years – it is a way of understanding its pathophysiology in order to think more holistically about how we approach cure and control. There's a complex interplay between developmental biology and evolutionary theory involving epigenetic mechanisms, cell populations and their ecology, i.e. the environment within which the cancer cells develop.

Can the principles of evolution be applied in practice?
Absolutely. Many organisms (bacteria, funghi, and so on) secrete substances to keep down the competition; cancer cells do the same. Cancer cells are in competition with each other and also with surrounding tissues for resources. Primary bowel cancers have an anti-angiogenic secretion which keeps down other metastatic growth and removing them can put the liver at risk of an explosion of metastases.

The evolutionary principles of selection and isolation can help us understand how cancer develops and the process by which metastatic cells – effectively in a new ecological niche – develop into a new 'species'. We can also consider cancer in terms of its 'fitness' and even how this works in terms of predation (by the immune system). Suboptimal traits that predispose people to cancer can usually be explained by evolutionary explanations which include constraints, reproductive advantage at the expense of the individual and defensives that are averse but useful.

Does evolution explain the burden of cancer?
Evolution has a sex-bias placing a higher importance on the female; male mortality from cancer is 3 times as high, because men are, by and large, not as 'valuable' in evolutionary terms! The 'grandmother effect' hypothesises that even old women live longer than men because they are more important to the fitness of the next generation.

The evolutionary theories of Darwin and others (notably Ernst Mayr and Niko Tinbergen) have heavily influenced cultural transmission theories; Richard Dawkins later described 'memes', or discrete packages of information transmitted down generations. Cultural theories address certain behaviours which increase cancer risk: smoking, drinking, over-eating. These behaviours may involve 'the thrifty gene' and are maladaptive in the current environment.

Understanding gene-culture co-evolution (Cavalli-Sforza et al.) is critical. Certain sets of genes might have increased fitness at one time, but become deleterious in the modern environment. For example, Sir Bruce Ponder and colleagues found that many breast cancers are caused by a combination of low penetrance genes. This background can increase risk 30-40 fold so these genes may have had other adaptive functions which trade off against an increased cancer risk.

How could Darwin's theories alter the way we approach treatment?
Chemotherapy and radiotherapy both aim to destroy cancer cells selectively, but the application of increasingly sophisticated mathematical models from evolutionary research will bring a fresh perspective to how we deliver complex regimens. Interactions between adaptive and selective processes using models of recursive causality can provide a different systems approach to applying the new generation of targeted agents.

Can theories be used in the clinic?
We see cancer as such a negative thing; but Darwin provides an easily understandable framework which can normalise and destigmatise cancer for patients. Darwin has suffered from intellectual elitism which needs to be ditched because evolutionary theory in fact allows us to explain in completely straightforward language, why things are the way they are. Evolution is fundamental to much of what we do; understanding more about Darwin's theories and those of the post Darwinian synthesis would be hugely beneficial both for stimulating new research ideas but also for education and communication.

Helen Saul