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'Global framework required' for research

Research policy needs a dedicated global framework, according to the authors of the second European Cancer Research Managers (ECRM) survey on European cancer research funding. The framework is needed to increase trans-national cooperation and to influence the political debate, they said.

ECRM chair, Professor Richard Sullivan, told *EJC* that a number of large funders, individual organisations and umbrella groups, operate on the same policy ground, and all consider research policy. But it is too often "tacked on the end" of reports covering cancer control and the immediacy of service delivery and treatment.

"If you look at the amount of time and effort spent on research as a policy issue, you find it is a sideline. There isn't actually any group or groups that take research policy as the main issue," he said.

Following the publication of the report (free to download at *www.ecrmforum.org*), he called for a global framework for cancer research. It could, to begin with, incorporate Australia, Canada, the US and Europe.

'RESEARCH POLICY IS A SIDELINE'

Improved co-operation is needed to increase trans-national funding of research, which will continue to grow in importance, as molecular biology breaks common cancers down into many different subtypes and "creates" more orphan diseases. Clinical trials requiring large populations will need to be carried out across borders, he said.

Its second function would be to influence politics. Professor Sullivan: "It is possible, despite our different views, still to have an integrated policy voice on issues that we all agree are dangerous. Everybody agreed that the Clinical Trials Directive was a disaster, yet we didn't get together and deal with it. We can't disengage from policy, it is too important. There has to be a better way of working together."

Professor Sullivan warned against the dangers of bureaucracy. The ECRM Survey found that, contrary to popular belief, European research output is on a par with that from the States. They looked at the volume of cancer research publications, and found that slightly more originate from Europe than from the US.

The US has higher funding but more bureaucracy, which increases the unit cost of research "in the absence of any tangible social benefit from many of these regulations," he said. "The US had ferociously more money than Europe, but it is several years ahead in terms of the bureaucracy burden. It is a warning. If Europe keeps on going down this route, with more regulation, regulation itself becomes the strategy. It's crazy."

Given this disturbing trend, the survey painted an encouraging picture. Pharmaceutical industry research is thriving in Europe, Professor Sullivan said, except for late stage clinical trials, which are mostly carried out in the States for marketing reasons. "Europe is strong in terms of industry publications. It is a myth that industry doesn't come to Europe."

Funding has increased by at least 18% over the 2 years since the previous study, with 9 Member States increasing their spending as a proportion of GDP. Some, such as Italy, Germany and France, could do more, Professor Sullivan said. France's new National Cancer Institute has been a step forward, but annual funding has only increased from Euro 239 million in the first survey, to Euro 249 million. "The organisation in France works, but there has not been a dramatic increase in funding. France produces a lot of research, but a little bit more money would improve things even further. We have said time and again that research and service delivery cannot be separated. If you want good service delivery, you need to be research active."

'WE CAN'T DISENGAGE FROM POLICY'

The UK, which has increased research funding, fared badly in the recent Eurocare-4 survey on cancer outcomes (*see over*). This is because the increase in funding started in 2001/2 and there is a lag before the benefit can be shown. "We will see things improving dramatically in the UK," Professor Sullivan said.

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Early drug design: Task force reports

Early trials of novel agents require a carefully tailored, individualised approach, a transatlantic task force reports in a forthcoming issue of *EJC*. An ideal trial design should be determined by features and expectations of the specific drug, they concluded. However, many of the assumptions underlying traditional presumptions remain valid.

The Methodology for the Development of Innovative Cancer Therapies (MDICT) task force was set up in response to the shift from traditional cytotoxic agents to molecular targeted therapies. Its aim was to outline the optimal approach in early drug development.

Dr Elizabeth Eisenhauer (National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario) said that, for example, many phase I studies still need to be designed to determine the full dose range possible for that drug i.e. find the maximum tolerated dose. Early hopes that non-cytotoxic agents would be non-toxic were not borne out by experience: "These agents have toxic effects associated with them; many produce toxic effects related to their mechanism of action, and very often the toxic effects limit how much can be given.

'ONCOLOGY SHOULD COME INTO LINE WITH OTHER FIELDS'

"Regardless of whether you choose to use the highest dose in subsequent trials, the phase I trial should, when possible, provide the data about what it is. Decisions about the recommended dose to take forward should incorporate this information, as well as other inputs, such as proof of principle data. Preclinical data on the targeted agents currently marketed have tended to show that higher doses are more effective, so, unless there is other contradictory information, knowledge of what the top dose achievable is in human studies is important."

In phase II trials, there is an ongoing debate about whether randomisation is necessary. Traditional agents were not tested in randomised trials, because the effect observed – tumour shrinkage – is highly unlikely to be related to the natural history of the disease, Dr Eisenhauer said. It may, however, be hard to interpret results of a trial of a novel agent – which leads to non-progression or stable disease – without a control group.

But she said trials should be designed for individual agents. "It is very dangerous to make sweeping statements on whether phase II trials should be or should not be randomised. It depends what question you are asking. If the question is more effectively answered with a randomised design, then it should be used."

Although tumour shrinkage was not expected to happen with novel targeted agents when they first were studied in the clinic, it has been seen with many, she said. If a new agent enters the clinic affecting the same target as another drug which was observed to produce objective responses, then it is reasonable to expect the new agent to also do the same and randomisation is not be necessary to detect this. "In that case, you can be reasonably certain that if you saw no evidence of response and rejected the drug for further development, you would probably be correct," said Dr Eisenhauer.

An editorial, in the same issue of *EJC*, called for a reduced role for non-randomised phase II trials. The editorial accepted that nonrandomised phase II trials "may be the only pragmatic option" in rare diseases, and acknowledged that they will continue to be used to determine the response rate to a single agent of unknown activity.

However, single-arm historically controlled phase II trials are rarely employed outside of oncology, and the editorial called for oncology to come into line with other fields. "We strongly recommend that randomised comparative phase II trials (with dose ranging as appropriate) become a standard approach in oncology, especially for the development of drug combinations," it concluded.

Eurocare-4

The gap in survival from cancer is narrowing across Europe, say the authors of a EUROCARE-4 report (*Lancet Oncology* 2007;**8**:773–783). The report was based on 2.7 million adult cancer cases diagnosed in 23 European countries in 1995–99. Overall survival has increased across the continent, which "suggests substantial improvement in cancer care in countries with poor survival."

However, differences remain. "If all countries attained the main survival (57%) of Norway, Sweden and Finland... about 12% fewer cancer deaths (about 150,000) would occur in the 5 years after diagnosis," the report concluded.

Nelarabine approved in Europe

Nelarabine solution (Atriance) has been approved in Europe for the treatment of T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL). The approval covers patients whose disease has not responded to, or has relapsed following, treatment with at least 2 chemotherapy regimens.

The European Medicines Agency (EMEA) granted nelarabine orphan drug status in June 2005. The new approval means that marketing authorisation is immediately valid in all 27 EU Member States, with identical national licences usually issued in Norway, Iceland and Liechtenstein. In the US, nelarabine has been marketed as Arranon since receiving FDA approval in October 2005.

Bevacizumab in lung cancer

Bevacizumab (Avastin) has been approved in Europe for the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC), in combination with any platinum-based chemotherapy regimen. The Vascular Endothelial Growth Factor (VEGF) inhibitor has been previously approved in Europe for first-line treatment of metastatic colorectal cancer and metastatic breast cancer.

Stem cell researchers 'face prosecution'

Issues of biomedical ethics do not fall with the competence of the EU, and until recently this was seen as a convenient way of getting round the difficulties of the varying views of member states on such things as embryo and stem cell research, and animal experimentation. Recently, however, cracks have begun to show in this approach, with scientists claiming that the lack of harmonisation can disrupt and delay research with important implications for human health.

First of all there was the narrowly averted blockade of the 7th Framework Research Programme. Failure to agree on whether or not human embryonic stem cell research should be funded looked likely to hold up the entire programme and leave the European Commission with no mechanism for supporting research at European level.

'WE CANNOT UNDERTAKE THIS WORK IN A WIDE SPREAD EUROPEAN COLLABORATION'

Now scientists are saying that the differing legislative positions on human embryonic stem cells (hESCs) in member states are having a highly deleterious effect on collaborative research, and indeed threatening researchers from certain countries with legal action simply because they are involved in a collaboration.

On 27 July, 2007, EuroStemCell and ESTOOLS, the two major EU-funded stem cell research consortia, issued a statement to MEPS in which they highlighted potential problems. Projects that are perfectly legal in Sweden and the UK can result in a three-year prison sentence in Germany, they say. And scientists from countries with restrictive legislation might even be liable to prosecution by taking a purely administrative, co-ordinating role where other collaborators are using hESCs.

The EuroStemCell and ESTOOLs projects comprise 29 research teams from academic institutions and biotechnology enterprises active in 12 states across the European Research Area. "These projects therefore represent a significant force for integrating and advancing Europe's R&D effort in stem cell research", says the statement.

Professor Peter Andrews, co-director of the University of Sheffield's Centre for Stem Cell Biology, says that he has personal experience of the problems that can arise. "German post docs in our lab are reluctant to work with cell lines derived after 2001 in case there are consequences for them when they go home. There are also two German partners in the ESTOOLS consortium who can only work on pre-2002 cell lines, whereas the rest of us are working on lines that are far more recent," he said.

Professor Andrews is one of the few cancer researchers to be currently working in the human embryonic stem cell field. "In order to provide differentiated cells for regenerative medicine, hESCs need to be maintained in culture for long periods. We noticed that hESCs in culture underwent the same kinds of karyotypic changes as occur in germ cell tumours, and we think that these changes reflect tumour-producing events *in vivo*, particularly in testicular cancer. Identifying the genes responsible for culture adaptation may thus reveal those that contribute to tumour development in humans and animals.

"We therefore believe that the study of hESCs holds out much promise for the understanding and treatment of cancer, and we are unhappy that we cannot undertake this in the kind of wide-spread European collaboration that we would wish. Laws forbidding scientists to work with hESCs derived after 2001 do nothing for human dignity or for progress in research. On the contrary, they hold up the development of novel biomedical therapeutic applications for their populations."

There are also problems in Italy, and in some of the newer EU member states. Although Italian law says that it is legal to work on already-established hESC lines from frozen discarded embryos but that it is illegal to derive new cell lines. However, this legal research is prevented by Italian public funding agencies, who only allocate resource for work on adult stem cells. Such 'financial punishment' goes against scientific evidence and the view of the international community, say Italian scientists.

German researchers are also calling for changes, notably the abolition of the cut-off date, permission to import cell lines from overseas for diagnostic, preventive and therapeutic purposes, and an assurance that scientists who are involved in international collaborations, or for working in overseas laboratories with cells that are not permitted in Germany, will not be prosecuted. Such changes are necessary to keep German research internationally competitive and to encourage young researchers to work in this exciting new field, they say.

'THERE ARE ETHICAL COSTS IN DELAYING THE FRUITION OF STEM CELL RESEARCH'

What are the real chances that any kind of harmonisation of national laws on this kind of ethical issue will ever be achieved? Practically zero, said a spokesman for DG Research; cultural, philosophical, and religious differences are so great that it would take a miracle to resolve them to everyone's satisfaction. So in the meantime, scientific progress will be held back and researchers will have to live under the shadow of prosecution.

"Wherever such fundamental questions or moral and human values are raised, the ensuing polarisation tends to become a minefield for politicians and decision-makers. Commonly the best way to survive in a minefield is not to move. But…… not moving also has a cost. And if one is serious about the ethical appraisal of stem cell research, one should at the very least consider the ethical costs associated with delaying the fruition of stem cell research's potential benefits", says the EuroStemCell and ESTOOLs statement.

Mary Rice
Brussels

Accuracy of US cancer surveillance under threat

Sharp reductions in cancer reporting by US Veterans Affairs (VA) hospitals will disrupt US cancer surveillance efforts, according to a report prepared by the California Cancer Surveillance Program (Sacremento, CA, USA). The report, obtained by *The Lancet Oncology*, details a precipitous decline in VA reporting of new cases to Californian cancer registries beginning in late 2004 – from 3000 cases in 2003 to almost none by the end of 2005.

"Crisis is not too strong a term", says Dennis Deapen of the Los Angeles Cancer Surveillance Program (Los Angeles, CA, USA). "Surveillance, geographic, or cluster information, and research mandated by law, will be affected."

"State-wide and national data will be incomplete and inaccurate", confirms Kurt Snipes of the Cancer Surveillance Branch of the California

'CRISIS IS NOT TOO STRONG A TERM'

Department of Health Services in Sacremento. Up to 5% of California's cancers are diagnosed in veterans, he notes, and in view of California's large population, national cancer statistics will also be affected. "It may falsely appear that prostate cancer incidence has declined across California and the US by at least 4%," says Snipes. Statistics for colorectal, lung, and bronchus cancers – and possibly myeloma, which is over represented in aging veteran populations – may also be affected.

Inconsistent and incomplete case reporting by VA hospitals are also longstanding problems for other US states. The Florida cancer registry has never received VA case reports, and VA facilities elsewhere are clearing backlogs of unreported cases. "We've been working with the VA for more than 5 years, but it's just got worse," says Holly Howe of the North American Association of Central Cancer Registries (NAACCR, Springfield, IL, USA).

On August 7–8, 2007, a group of officials from the NAACCR; US state and regional cancer registries, the US National Cancer Institute (NCI; Bethesda, MD, USA); the Centers for Disease Control (CDC; Atlanta, GA, USA); and the American Cancer Society (ACS; Atlanta, GA, USA) met in Chicago, IL, USA to discuss the situation.

"We will not get VA case data in time for next year's statistical reports," says Dee West of the Northern California Cancer Center (Fremont, CA, USA). "Now we are talking about how to publish cancer rates."

Speaking at a NAACCR meeting in September, 2006, Deapen warned that the omission of veteran data would

'WE ABSOLUTELY MUST HAVE VA DATA FOR SURVEILLANCE PURPOSES'

introduce "uncorrectable bias" in epidemiological studies. "Research from the mid-2000s will forever require an asterisk," he predicted, "to remind researchers and the public that they are not correct."

Raye Ann Dorn, the VA's national coordinator of cancer programmes, told *The Lancet Oncology* that only registries in California and Florida are not receiving VA cancer-case data. However, several other US state registries contacted for this report also noted disruptions. Reda Wilson at the CDC says that in 7 US states, VA facilities are not reporting cancer cases, and in 6 other US states, at least one VA facility is not reporting.

Several of the affected registries participate in the NCI's Surveillance Epidemiology and End Results (SEER) programme, providing data with which national cancer rates are estimated. "This will significantly impact reporting in SEER," says Brenda Edwards at the NCI.

US States have no jurisdiction over federal hospitals, so VA case reporting is voluntary. VA officials point out that of the 130 medical centres that collect cancer data, only 29 withheld cases from state cancer registries in 2006.

According to state registry officials, however, VA facilities that do report cancer cases increasingly prevent registries from conducting data completeness or quality audits. "We cannot get into VA facilities now to check records and make sure all cases are reported," says West.

Surveillance efforts will also be complicated by new VA rules against data sharing between US states. Veterans are routinely sent across US state borders to larger or more specialised VA facilities. "But the VA is no longer allowing states to exchange veteran case data," says Kohler.

The VA views the release of veterans' cancer data to epidemiologists – and researcher contact with veterans – as potential intrusions on patient privacy. Curiously, only cancer data seems to have been affected.

A new VA policy directive on cancer reporting is due out later in 2007, nullifying all existing agreements between state registries and VA facilities. A draft version obtained by *The Lancet Oncology* reveals that the directive will formalise the prohibitions on the sharing of veteran cancer data between states and will forbid the "re-release" of veteran data to researchers whose studies have not been approved by the VA.

"The Directive is not restrictive," insists Dorn, "but does impose safeguards for protecting VA patients from inappropriate disclosures, requires no contact with veterans, and prohibits the re-release of data."

Such rules will hamper research, argues Deapen. Ascertaining exposures, experiences, and survival issues involves patient contact. "Researchers need to contact patients," he says.

But Snipes reports that the California Central Cancer Registry is willing "for the time being" to forego sharing data with researchers if doing so secures renewed VA case reporting. "We want to keep working on being able to use VA data for research, but we absolutely must have their data for surveillance purposes," he explains.

Elizabeth Ward of the ACS remains hopeful that a compromise can be achieved. "I think we need everybody in the room at one time – medical, epidemiological, and legal experts," she says. "We need to work together to move ahead."

Bryant Furlow

The full version of this story appears in Lancet Oncol 2007 **8**:762–3

PODIUM

Elderly patients: the forgotten majority

Riccardo Audisio is a consultant surgical oncologist and honorary reader (University of Liverpool, UK), and editor-in-chief of Surgical Oncology. His clinical research focuses on geriatric oncology and he chairs SIOG's surgical task force. He is a guest editor of the EJC Special Issue 'Cancer Management in the Elderly: A Progress Report'

Do elderly patients have special requirements?
Different approaches are needed from standard care; this is a key message. Geriatric oncology needs to attract interest, money and enthusiasm in a way similar to – but on a much larger scale than – paediatric oncology. Paediatric oncology represents a minute percentage of cancer; geriatric patients account for 60% of all cancer deaths. It is an epidemiological time bomb, an emergency, and people should be aware of it.

What do elderly patients need?
Technically speaking, there is no data on how best to manage the elderly. In the 1980s, epidemiologists observed increasing numbers of elderly patients; they also noted that diagnoses were inadequate, staging substandard, and treatment far from optimal. Medical oncologists did not enter elderly patients into trials, so we don't have hard knowledge on the best treatment. This is also true in surgery: the original Veronesi/Fisher study comparing lumpectomy with mastectomy had a cut off point at 70 years. There is confusion. We don't want to over-treat frail patients, but, equally, we don't want to under-treat just because someone is elderly.

How do elderly patients differ?
In medical oncology, the pharmacokinetics and pharmacodynamics are different. Patients are often taking multi-drugs, so drug interference is possible; oncologists do not want to induce toxicity. Similarly, elderly patients react to surgery in a different way. And they occasionally can't comply with radiotherapy: either they can't squeeze into the machine or they have no transport to get to the radiotherapy unit.

Given that 2/3 of cancer affects elderly people, it is surprising that we don't know how best to handle them surgically or medically. We assume that what is delivered to younger patients will be appropriate. It is shameful that we don't put the effort into providing the care we give younger cancer patients.

Is there ongoing research?
We have come a long way in the last 10 to 15 years. Since then, the Comprehensive Geriatric Assessment (CGA) has been suggested and there are trials which will allow us to offer the best treatment according to patient's sickness.

How well known is the CGA?
Not sufficiently, and hardly at all in surgery. Without it, someone with cancer who could withstand surgery may not be offered it; someone else may be judged fit enough, where the CGA would have revealed comorbidities such as depression or malnutrition. The CGA is derived from a more detailed geriatric tool. It is pragmatic, easy, and sufficiently reliable.

Do we need to increase the age limit in clinical trials, or set up age-specific trials?
Both. There is increasing evidence that medical or surgical treatment should be delivered to elderly patients who are fit enough; hence the value of the CGA. But where a frail subset of patients requires drugs which do not induce toxicity, we should develop age-specific investigation. Because 78% of elderly people take multiple medicines, drug interactions are a problem. But we can't avoid involving these patients in trials. There is no point discovering that a drug works beautifully alone when in clinical practice, it is to be taken with several other drugs.

Is best clinical care more important than novel agents in this group?
Quality of life has to be a priority. You can't always increase life expectancy in this older group. Life comes to an end, and you must be sure that you are not imposing an unacceptable treatment which extends survival by a few months but results in an intolerable quality of life.

Has the notion of QALYs led to discrimination?
Yes! I've even heard talk of active life expectancy, implying that those who are not active don't deserve survival benefit. Society thinks that the rich, beautiful and young warrant care; and the ugly, poor and elderly, probably don't. I don't subscribe to this. These people have been paying taxes all their lives and are entitled to the best treatment. You see old people sailing through treatment and 3, 5 or 10 years later, are still happily dealing with their grandchildren. Society benefits from this.

Are there differences in treatment approaches across Europe?
There are differences in cancer management, but not strikingly according to country. The elderly are similarly mistreated across Europe, the US and Japan. We are all making the same mistake.

What do you hope the Special Issue will achieve?
We want to raise awareness among the public, health care providers and politicians. The only way forward is to create geriatric oncology units which will optimise the management of cancer in the elderly. Only 3 currently exist in the world.