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Cancer Control in Africa

Immediate action to bring comprehensive cancer care to African countries has been called for. The so-called London Declaration states that 'With concerted early action, cancer in Africa is a disease that can be tackled.'

The declaration was presented at the Cancer Control in Africa meeting (May 10–11, 2007, London, UK). The health ministers of 22 African countries attended the meeting, along with delegates from the World Bank, the World Health Organization, the African Development Bank and leading oncologists. The Gates Foundation, the pharmaceutical industry and major cancer organisations and charities were represented.

The meeting was organised jointly by the newly-formed Africa-Oxford Cancer Consortium (AfrOx) and the International Atomic Energy Agency (IAEA), which runs a Programme of Action for Cancer Therapy (PACT). Professor David Kerr (Oxford University, UK, and AfrOx) said that more than 70 percent of all cancer deaths already occur in low and middle income countries. 'This figure is rising due to increased life expectancy, increased tobacco use and chronic viral infection.

The UK's Secretary of State for Health, the Rt Hon Alan Milburn MP said that 'Africa will be particularly hard hit because it lacks the basic infrastructure to cope with a big growth in cancer in the years to come. If we can pool expertise and resources we can save tens of thousands of lives.'

The declaration calls on research institutions, international organisations, the pharmaceutical industry and national governments and civil society in developed and developing countries 'to unite and work together to bring comprehensive cancer care to Africa.'

Pooling expertise and resources: Front row (left–right): Professor Sir John Arbuthnott, UK; Dr. Innocent Nyaruhirira, Rwanda; Dr. Basilio Mosso Ramos, Cape Verde; Mrs. Abator Thomas, Sierra Leone; Dr. Motloheloa Phooko, Lesotho; Professor Paulo Ivo Garrido, Mozambique. Back row (left–right): Professor David Kerr, UK; Mr. Massoud Samiei, PACT; Dr. Catherine Le Gales-Camus, World Heath Organization; Professor Werner Burkart, IAEA; Dr. Mohamed Youssouf, African Development Bank.

It outlines six essential steps:

- Cancer surveillance programmes and national cancer plans.
- Prevention programmes. Almost 40% of the cancer deaths in sub-Saharan Africa can be explained by chronic infection and tobacco use.
- Early diagnosis and screening programmes.
- Effective treatment programmes and access to radiotherapy facilities.
- Palliative care.
- Training and research. International cancer institutes should establish mentorship and training programmes for African health professionals and scientists; new local healthcare personnel must be trained to increase capacity.

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Molecular targets and cancer therapeutics

Metronomic chemotherapy can be surprisingly effective, Professor Robert Kerbel (Sunnybrook Health Sciences Center, Toronto, Canada), told the 18th Symposium on 'Molecular Targets and Cancer Therapeutics' (*November 7–10, 2006; Prague, Czech Republic*).

The symposium, which was organised by the European Organization for Research and Treatment of Cancer (EORTC) in conjunction with the US' National Cancer Institute (NCI) and the American Association for Cancer Research (AACR), heard that metronomic chemotherapy entails regular administration of low dose conventional chemotherapy drugs, in the absence of any prolonged drug-free break periods, over long periods of time, even several years. Unlike 'dose-dense' intensive chemotherapy, it is minimally toxic and thus does not usually require supportive care drugs.

Metronomic chemotherapy is especially effective when used in combination with a targeted antiangiogenic agent. Its anti-tumour effects are thought to be due mainly to anti-angiogenic mechanisms through local targeting of dividing endothelial cells in the growing tumour neovasculature, and also due to the systemic targeting of bone marrow-derived circulating endothelial progenitor cells (CEPs). Maximum tolerated dose (MTD) chemotherapy may, in some circumstances, also target CEPs, but a haemopoiesis-like pro-angiogenic acute CEP 'rebound' can occur immediately afterwards and nullify the effect. Shortening or eliminating drug-free periods may prevent the rebound.

Certain antiangiogenic drugs such as bevacizumab enhance the efficacy of some conventional chemotherapy regimens. It could be that the anti-angiogenic drugs are preventing the systemic CEP rebound.

Determining the optimal dose of the chemotherapeutic agent is problematic but the discovery of surrogate markers to monitor biologic activity of metronomic chemotherapy may help. These markers include circulating apoptotic endothelial cells and CEPs.

● **Phase 0 trials** could accelerate the development of new drugs, said Dr. Chris Takimoto (Cancer Therapy and Research Center, San Antonio, USA). They are low-dose studies performed prior to conventional phase I studies, and have no therapeutic intent. A phase 0 study could involve micro-dosing of single or multiple agents and pharmacokinetic and pharmacodynamic studies with new biochemical or molecular biomarker endpoints. The objective is not to reach a maximally tolerated dose or therapeutic benefit, but to collect data on bio-availability, toxicities or molecular markers. Phase 0 trials would allow early screening of potentially active and non toxic drugs and of biomarkers of efficacy.

● **The RECIST criteria** (response evaluation criteria in solid tumours) are validated and widely used but have limitations, according to Dr. Patrick Therasse (GlaxoSmithKline Biologicals, Rixensart, Belgium). There are delays in identification of progression (in some instances) when compared to WHO criteria, difficulties related to the measurement of the size of lesions (such as in paediatric trials or in mesothelium), and difficulties encountered when anatomical changes occur later than functional changes (as shown in GIST trials). A revised version of the criteria is being developed by the RECIST working group, with more emphasis on new functional imaging techniques and specific criteria for particular tumour types.

● **Randomised phase II** studies are needed to evaluate the combination of tyrosine kinase inhibitors (TKIs) with established treatment regimes, Professor Mark Ratain (University of Chicago, USA) said. Most phase I studies do not establish whether the TKI enhances the toxicity of the chemotherapy. Randomised phase II studies which compare the combination of TKI plus chemotherapy with chemotherapy alone, could avoid negative phase III studies, he said.

● **A promising anti-apoptosis agent** has been found to have a short half-life. The human recombinant (rh) Apo2L/TRAIL has been relatively well tolerated and shown promising activity in a variety of solid tumours and haematological malignancies. However, preliminary pharmacokinetic results have revealed a very short half-life, according to Dr. Avi Ashkenazi (Genentech, South San Francisco, USA).

TRAIL is a naturally occurring death receptor ligand which can selectively induce apoptosis in tumour cells by binding to its cell membrane death receptors DR4 and DR5. Agonistic antibodies against DR4 (mapapumumab) and DR5 (lexatumumab) have displayed a much longer half-life, than (rh) Apo2L/TRAIL. Several studies of these are underway.

● **The eukaryotic elongation factor-2** (eEF-2) kinase plays a regulatory role in the autophagic process in tumour cells, according to Professor William Hait (R. W. Johnson University Hospital, New Brunswick, USA). Autophagy is a cellular process that enables cells to turnover their content and is initiated in response to nutrient and growth factor deprivation, or other forms of cellular stress such as chemotherapy or radiation in tumour cells. It has not been known whether this contributes to tumour cell death or helps tumour cells survive the anticancer therapy.

Recent preclinical studies showed that eEF-2 kinase promoted cancer cell survival under conditions of nutrient deprivation through regulating autophagy. eEF-2 kinase may therefore be part of a survival mechanism and targeting this kinase may represent a novel approach to cancer treatment.

● **The metastatic process** may be targeted via the metastasis suppressor protein KISS-1, according to Dr. Danny Welch (University of Alabama, Birmingham, USA). He demonstrated that KISS-1 expressing cells are able to go through all the phases of the metastatic process but are unable to proliferate at the metastatic site, where they remain quiescent. KISS-1 is involved as a metastasis suppressor in breast, ovarian, stomach, thyroid, endometrial and bladder cancers as well as mela-

Molecular targets and cancer therapeutics

noma and could be a therapeutic target for the management of metastatic disease, he said.

Hypoxia is involved in the metastatic process and a high incidence of metastatic disease is seen after surgery of a hypoxic primary tumour. Furthermore, preliminary exposure of cancer cells to hypoxia *in vitro* before *in vivo* transplantation raises the risk of metastasis. Hypoxia, via hypoxia-inducible factor 1 (HIF-1), induces transactivation of many genes whose protein products either increase oxygen availability or allow metabolic adaptation of oxygen deprivation, in particular proteins involved in erythropoiesis, glycolysis and angiogenesis. These proteins provide many targets for antiangiogenic therapy.

● **Melanoma vaccination trials** using monoclonal antibodies targeting CTLA4 have shown promising results. CTLA4 (cytotoxic T-lymphocyte antigen 4), a receptor on dendritic cells, is a down-regulator of the immune response. As a molecular target, it may allow the enhancement of the immunologic recognition of tumour cells.

Dr. Jeffrey Weber (University of Southern California, Los Angeles, USA) presented data on MDX-010, a human monoclonal antibody specific for CTLA4. Response rates of up to 22% have been demonstrated, lasting for 12 months, in melanoma and renal cell carcinoma. Auto-immune reactions correlated with tumour response.

● **Cancer stem cells** share the property of unlimited growth potential and self-renewal with normal stem cells. Solid tumours consist of a heterogeneous population of cancer cells which differ in their apparent state of differentiation, suggesting that solid tumours might represent aberrant organs containing a cancer stem cell population that maintains the ability to self-renew. Indeed, Professor Michael Clarke (Stanford Institute for Stem Cell Biology and Regenerative Medicine, Palo Alto, USA) and colleagues have identified small populations of cells within breast tumours that can be defined as cancer stem cells and have the exclusive ability, when transplanted, to form tumours. Similar observations have been made with transplanted primary acute myeloid leukaemia (AML) cells.

Moreover, the gene signatures of stem cells have prognostic power: breast cancers showing a gene expression signature that includes stem cell specific genes have a poor prognosis. The prognosis becomes worse when combined with a wound repair signature. It is therefore critical to understand whether current therapies target stem cells and whether targeting cancer cell self-renewal pathways will result in more effective cancer therapies.

Tumour cells and embryos have antigenic similarities and Professor John Eaton (University of Louisville, USA) tested the idea that vaccination with embryonic stem cells (ESC) would prevent tumourigenesis. In 2 separate models of lung cancer, vaccination with allogeneic ESC provided protection against tumour outgrowth. The work raises the possibility of a prophylactic vaccine capable of preventing various cancers in humans.

● **The new 'omics' techniques** – genomics and proteomics – may aid the discovery and development of new drugs, according to Professor Paul Workman (The Institute for Cancer Research, Sutton, UK). Proper use of biomarkers can make clinical trials more intelligent and informative, and decision making more rational and effective, he said. A 'pharmacologic audit trail' has carefully planned preclinical and clinical phases, and may allow early evaluation of the risk of failure. A series of questions has to be answered during drug development: What is the status of the molecular target? Is the drug concentration sufficient in the plasma or tumour? Is inhibition of the molecular target obtained? Or is there a modulation of the biological pathway? Is the biological effect reached and does it translate into a clinical effect? As a drug progresses through the hierarchy of questions, the risk of failure is reduced. It is therefore essential to have robust validated assays available for molecular biomarkers and pharmacokinetic behaviour.

Biomarkers need to be carefully evaluated in randomized trials designed to prove their clinical utility, said Professor Ratain. These trials are often neglected, especially by industry, because of their low direct commercial impact. Biomarkers are nevertheless widely used in the clinical setting where their sensitivity, specificity, and positive/negative predictive value are well characterized.

● **Functional imaging methods** are widely used to facilitate early clinical PK/PD assessments, measure surrogate functional endpoints and assess drug efficacy. Current research programs focus on quantification of signals, reproducibility, and quality assurance. Large clinical trials are systematically evaluating imaging.

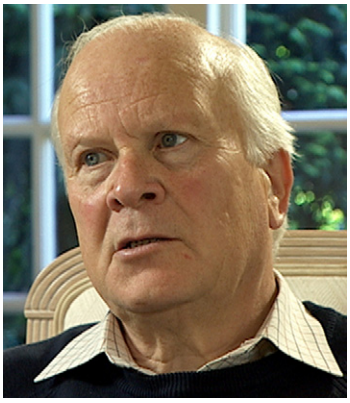
Further progress will come from the development of novel imaging strategies. Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) has been used to evaluate anti-VEGF antibodies and receptor TKIs in phase I clinical trials, said Professor Gordon Jayson (Christie Hospital, Manchester, UK). The rationale is that if such drugs are working as predicted then local reductions in vascular permeability should be seen. Multiple trials suggest that the magnitude of the reduction in vascular permeability correlates with the dose of the drug, and that the magnitude of reduction is related to stabilisation of the disease. However, tumour masses usually have a ring-enhancing pattern suggesting that there is considerable heterogeneity across a tumour, which is clinically significant, according to recent studies.

Professor David Piwnica-Worms (Washington University School of Medicine, St-Louis, USA) described an imaging strategy using genetically-encoded imaging reporters introduced into cells. The technique allows the assessment of signal transduction and protein-protein interactions and has the potential, eventually, to translate into the clinic.

Lucile Serfass (EORTC, Brussels, Belgium); Carla Van Herpen (Radboud University Nijmegen Medical Centre, the Netherlands); Mahasti Saghatchian (Institut Gustave Roussy, Villejuif, France).

PODIUM

A lifetime in breast cancer research



Michael Baum, Professor Emeritus at University College London, UK, has devoted his career to the research and treatment of breast cancer. A general surgeon by training, he was an early proponent of breast conserving surgery, and more recently, ran trials of adjuvant tamoxifen, and anastrozole (ATAC). At the recent St Gallen Breast Cancer Conference (March 14–17, Switzerland), he received the Lifetime Achievement Award.

What does this award mean to you?

It is the most important honour I have received. Previously the most important was the William McGuire award (for lifetime achievement in breast cancer research, given at the San Antonio breast cancer symposium in 2002). It was very nice to be recognised in the US but to receive a biennial international award trumps that. What makes me most proud is the luminaries who have received it in the past – Bernie Fisher, Gianni Bonadonna and Umberto Veronesi – it is wonderful to be named in that lineage.

What do you see as your greatest achievement?

I suppose I'm best known for my work on adjuvant tamoxifen and adjuvant aromatase inhibitors. These results have influenced treatments. Then there's all the unspectacular work that no-one appreciates: for example, establishing the principles of clinical trials and of collaborations, the ethics of informed consent, and so on. I set up the first clinical trials centre in Europe. This work gets no recognition, but without the infrastructure for clinical trials, nothing else follows.

My generation established this infrastructure and it won't need to happen again; we were the pioneers of multicentre, international clinical trials. The infrastructure now exists for a new generation to exploit. But they face a new set of threats: the EU directive on clinical trials is destroying much of the good work done in the past.

What are the landmarks in your career?

Breast conservation was one of the first. I don't want to claim too much credit because most of the clinical trials were carried out in Milan, and by Bernie Fisher in the States. But some credit for challenging the concept of radical surgery. I was one of the most outspoken people at the time, challenging the principle – dogma – of radical surgery. Going back 30 or 40 years, this was heretical, and made me very unpopular. My group was unable to recruit very well for our own breast conserving trial; it was described by a journalist as the trial everyone needed and no-one wanted. In the end, we abandoned it after 150 patients but with these patients we measured the psychosocial outcomes associated with mastectomy versus breast conserving surgery.

You have often found yourself in the midst of controversy?

I have never ducked controversy. It's not that I embraced it; it's just that something in my personality will not compromise on scientific integrity. Too many people seek instant popularity by compromising their scientific integrity. If you want to make an important advance, forget popularity, you may become popular in the long run, but don't bank on that in the short term.

My wife is distressed by my current unpopularity for condemning homeopathy. But you have got to be prepared to say it's a lot of nonsense.

Your stance on screening is another case in point?

I have devoted my life to women's health, but along the way I have always believed you must treat women with respect. What I find incredibly distasteful about screening is that women are socially engineered to do what the agents of the state want them to do. The screening establishment wants women to be compliant and I believe has been parsimonious with the truth in the screening invitation. You must get informed consent, so the invitation must be formed in language women can understand. The absolute benefits should be made clear: you have to screen 1000 women for 10 years for one life to be saved. That life is of infinite value, but along the way there are harms and women must be alerted to the harms: false alarms, over-diagnosis, borderline pathology, ductal carcinoma in situ, breast cancer which, if left untreated, would never present clinically.

It's a false premise that if you catch breast cancer early you will save the breast, because mastectomy rates increase in absolute terms where there is screening. Women deserve to know all this. If they elect not to come, that's their privilege.

In fact there's a J-shaped curve in screening attendance according to educational level. The most ignorant women don't come for screening because they are probably not interested in health promotion. But the most well-informed don't come either as they see through it all. Now that's very interesting.

Screening is also a very inefficient way of dealing with the problem. I can't believe it's cost effective for the UK to spend £70 million (approx €105 million) per year on screening, when we don't have the money for drugs like the aromatase inhibitors. It's frankly barmy.

PODIUM

You were involved in the key trials of these drugs

My group was the first to show the benefits of tamoxifen; I led the NATO (Nolvadex adjuvant tamoxifen) trial. We found an improvement in overall mortality but could hardly believe it. It wasn't until I sat down with Richard Peto to do the first meta-analysis, that we had absolutely unequivocal evidence. It was 1985 and I was then convinced we had something that would save lives. The atmosphere was electric when the results were first presented. The results – on adjuvant chemotherapy as well as tamoxifen – went round the world at the speed of light and were implemented everywhere within a year, leading to an incredible change in mortality – a 30% reduction.

Age-adjusted mortality had been going up and up. It plateaued in 1985, then dropped. There has never been a change in cancer treatment that gave such a striking appearance on the mortality curve. It was a seminal moment in the history of cancer research.

Our success was shared with many groups around the world and is probably the most important contribution to breast cancer survival of all time. The aromatase inhibitors are doing a little better but it's incremental. Tamoxifen was the big leap forward.

You also led ATAC

I was privileged to be at the Royal Marsden in the mid 1990s working with Mitch Dowsett, Ian Smith, and Trevor Powles. The basic work suggested that anastrozole was a promising drug, and we were using it in advanced cases. In setting up ATAC (Arimidex, Tamoxifen, Alone or in Combination), we decided to bypass the conventional route (of looking at the drug in trials of advanced cancer) and use it in early cancer for adjuvant therapy. I felt very confident of the principle behind this drug, its safety profile and ease of use, but this was a risk. In the event, it gave us a 2 year lead on everyone else.

At the first analysis, before giving the results, Jack Cusick asked the committee to take a vote as to which arm would be best: a third went for tamoxifen, a third for anastrozole and a third for the combination. That demonstrated the equipoise of the committee. But the combination arm looked unpromising and was closed down (in retrospect, there was a biological rationale for why the combination wouldn't work). When the results came up (showing an advantage for anastrozole), we were jubilant.

Where does your current research interest lie?

I'm the principal investigator in the TARGIT (Targeted intra-operative radiotherapy) study and I'm very excited about that. This is my baby; I have been involved in the research and development from beginning with a biotech company, the PhotoElectron Corporation. We talk about treatments for which there is no known disease; this was a device for which there was no known disease. It is an electron generator, a technique for intra-operative radiotherapy. I did the first case at University College, London, 8 or 9 years ago. Now TARGIT is a multi national trial, comparing one shot intra-operative radiotherapy, given by the surgeon, with a standard 7 week course of postoperative radiotherapy. We have recruited nearly 1000 women.

If it comes off, it will be a tremendous revolution. It will save women the time and trouble of making 42 visits to the radiotherapy centre. It will save £17 million (€25 million) / year in costs in this country – the equivalent of about one third of the radiotherapy budget. It is also a simple technology which could be used anywhere in world. It would make breast conserving therapy available to all women with breast cancer. At present, if you can't get to a radiotherapy centre because of the distance, or resources available, you can't have breast conserving surgery and have to have a mastectomy. So if the patient can't get to the radiotherapy centre then why not bring the radiotherapy to the patient?

What other aspects of your work would you like to mention?

Psychosocial oncology. I have just stepped down as chair of the Psychosocial oncology clinical studies development group at the UK's National Cancer Research Institute. We developed the first psychometric instruments for measuring quality of life, which involved promoting communication skills, and counselling. It all adds up to an improved quality of life. It is one of the more important threads in my life, and is what is meant by patient-centred care, but it doesn't hit the headlines. We hear a lot of nonsense about patient-centred medicine by politicians. But patient-centred medicine can and should be evidence-based.

What advice would you give to a newly qualified doctor?

Make up your mind whether you going for money and prestige or for a spirit of enquiry. For money you need to go into private practice. For a life of enquiry and excitement, go into academic medicine, there's nothing like the buzz. If you elect for academic medicine, take a subject where the disease is common and in which everyone agrees they know everything there is to know. This is fertile ground for research because it is never so. The whole history of science is an approximation of the truth. You should always search for the flaws in the assumptions when most people agree that there are no unanswered questions left. It doesn't make you popular, but it is a lot of fun!