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Young oncologists affiliate to FECS

The Flims Alumni Club (FAC) became an officially affiliated member of FECS (Federation of European Cancer Societies) in June, 2004, following a unanimous decision by FECS Council members.

Dr. Razvan Popesceu, President of FAC, said, ''FECS is the natural habitat of FAC – itself a multidisciplinary, dynamic group seeking to develop synergies across disciplines in clinical practice and research. Membership will open areas of involvement for a host of young clinicians and investigators, keen both to bring in their own vision and be mentored by those already serving European oncology – all sharing the goal of improving outcomes for cancer patients and fighting its causes''.

Ms. Kathleen Vandendael, Executive Director of FECS, said she was delighted by the move. ''It brings together two organisations which promote multidisciplinarity and fit perfectly together. FECS has long recognised the particular role played by young oncologists in shaping the future of the European Oncology Community. FAC's membership is an obvious means of enhancing our relationship, fostering co-operation and moving towards the future''.

''FECS IS THE NATURAL HABITAT OF FAC''

FAC was established in 2001 during ECCO-11, and its members are all past participants in the Flims Workshop on Methods in Clinical Cancer Research. It is, in effect, a network of young, mainly European, oncologists; 2 years after its foundation, FAC had a membership of 102 oncologists from 18 countries, with a mean age of 36. Most have already joined a discipline-based society and, following the affiliation, FAC's statutes will be altered to make this a pre-requisite for membership.

Since its inception, FAC and FECS have been eager to strengthen their links, and the move will help to achieve this. FAC will gain access to political information and all other services provided by FECS to its affiliated members. FECS will gain access to determined and active young people and the organisations expect to go on to develop joint activities.

To date, FAC has organised symposia and activities at major European meetings, with strong support from FECS and its member societies. FAC members already collaborate with young oncologists from member societies – such as with the ESMO Young Medical Oncologists – and the affiliation will promote further cooperation.

Members of FAC will have the opportunity to become involved, through FECS, in cancer-related politics, communication, education, and so on. For example, FECS has developed relationships and interactions with European institutions in order to raise awareness of oncology-related issues and influence the political agenda. One instance is the formation of an ad hoc research and development Working Group. It will develop a position paper for FECS, aimed at ensuring that an adequate budget will be allocated for cancer research in the 7th Framework Programme. Further, FECS is frequently contacted by various DGs to suggest the names of experts who could participate in various activities.

''IT IS A WIN:WIN SITUATION''

FECS is committed to communicating directly with patients' associations, national cancer leagues and the lay public and relies on experts from each member society to provide news of their field. FECS also aims to keep all members updated about developments in other fields and produces a quarterly newsletter sent electronically to all members. FAC President, Dr. Razvan Popescu was recently nominated editor-in-chief of the newsletter.

''Members of FAC will have the opportunity to become active in all of our initiatives. In return, FECS will be able to provide help with their issues and projects. The affiliation is a win:win situation,'' said Ms. Vandendael.

EJC's Impact Factor – up again!

The latest Impact Factors show that *EJC* has continued to build on previous success. The figures, released by the Institute for Scientific Information (ISI) in June 2004, put *EJC*'s Impact Factor at 3.694, maintaining its position ahead of titles including *Annals of Oncology* and *International Journal of Oncology*.

EJC's Impact Factor has risen year-on-year since 1999, when it stood at 2.537. *EJC*'s Editor-in-chief, Professor John Smyth said he was absolutely delighted. ''This reflects the quality of the papers submitted, and the enthusiasm of the European cancer research community for publishing in a European journal.''

Dr Peter Harrison, *EJC* Publisher, said, ''It is gratifying that all the time and effort expended by everyone in the *EJC* editorial team has paid off with this encouraging and sustained growth in our Impact Factor.''

EJC News is compiled by:
Helen Saul
Tel: +44 (0)1865 843340
Fax: +44 (0)1865 843965
E-mail address: h.saul@elsevier.com

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Highlights from 18th EACR Meeting 3–6 July 2004, Innsbruck, Austria

Chemoradioimmunotherapy: the future?

A novel technique to kill metastatic breast cancer cells by circumventing their chemo- and radioresistant mechanisms was presented at the meeting. Dr. John Giannios (IASO Hospital, Athens, Greece) described an immunotherapy regime aimed at blocking the genetic mechanisms that often protect cancer cells from conventional treatments *(Proc Eur Ass Ca Res 2004 297 Abs # 499)*.

Dr. Giannios' team analysed metastatic tumour tissue taken from patients with advanced breast cancer. They searched for over expression of known oncogenes such as HER-2, which enable cells to develop resistance to treatment with radiation and chemotherapy. They also detected over expression of DNMT1 (a DNA methyltransferase, involved in DNA replication and implicated in cancer development), and methylation of BRCA1 promoter (implicated specifically in the development of breast cancers).

The 3-pronged treatment comprised vinorelbine-tartrate chemotherapy, high energy radioisotopes and immunotherapy. The immunotherapy prevented cancer cells from evading the cytotoxic effects of treatment. It comprised: radio-labelled antibodies targeted to HER-2; along with a 21-nucleotide double stranded small interfering RNA generated against DNMT1.

Post-treatment, there was clear evidence that treated tumour cells were undergoing significantly more apoptosis than untreated controls. Apoptosis was confirmed by activation of the enzyme caspase-3-9; inhibition of DNA synthesis and metabolic activity in the tumour cells; formation of apoptotic bodies. These apoptotic bodies were seen to be phagocytosed by adjacent tumour cells, which resulted in the subsequent apoptosis of the tumour cells through a bystander killing effect.

Several diagnostic tests demonstrated that the novel regime had specifically impacted on the identified oncogenes. HER-2 was down regulated as a consequence of the action of the anti-HER-2 antibody; the tumour suppressor gene BRCA1 was re-expressed as a consequence of the inhibition of the DNMT1 mRNA; and the radioisotopes induced DNA double-strand breaks in the tumour cells.

Dr. Giannios' said the novel regime targeted and damaged by the chemotherapy and radiation therapy. It has potential as a tailored and targeted anti-cancer treatment which would reduce systemic toxicity and enhance the therapeutic index. 'These results open the possibility of combining targeted immunotherapy with chemotherapy and radiation therapy to successfully kill metastatic tumour cells,' Dr. Giannios said, 'Theoretically this novel technique should be as effective in other types of cancer that are characterised by hypermethylation of tumour suppressor genes and the over expression of oncogenes such as HER-2 and bcl-2. Our next step will be to develop the treatment in patients, and on a bigger scale, in a Phase I clinical trial.'

New kinase inhibitor shows promise

A novel compound combines inhibition both of tumour cell growth and of angiogenesis, the meeting heard. Dr. Gerhard Siemeister (Corporate Research, Schering AG, Berlin) described the actions of the chemically synthesized small molecule, an ATP-competitive kinase inhibitor, known as ZK-CDK *(Proc Eur Ass Ca Res 2004 289 Abs # 479)*.

The compound inhibits a range of cyclin-dependent kinases (CDK) involved in cell cycle control. It also inhibits molecules known to be involved in tumour angiogenesis: vascular endothelial growth factor (VEGF)-receptor tyrosine kinase (VEGF-RTK); and platelet-derived growth factor (PDGF)-RTKs.

ZK-CDK was tested on mice as an oral preparation, and was shown to inhibit the proliferation of human tumour cell lines. It blocked cell cycle progression in G1 and induced apoptosis, blocked VEGF-induced vascular permeability *in vivo* and reduced the blood supply of human tumour xenografts.

Dr. Siemeister said, 'These animal data are very promising in terms of anti-tumour efficacy and tolerability. The CDK inhibiting mechanism of ZK-CDK, in contrast to cytotoxic chemotherapy, should arrest the proliferation of normal cells but not kill them, allowing them to recover during drug-free cycles.'

The compound showed efficacy against both solid and haematological tumours but was particularly efficacious in slow-growing, hormone-independent, p53-negative models such as advanced, anti-hormone refractory breast and prostate tumours. It has entered phase I clinical trials.

Ancient skeletons reveal little cancer

Skeletal remains dating from 5300 BC to the 19th Century show little evidence of cancer and reinforce the concept of it as a modern disease, say Croatian researchers. They examined the remains of the 3160 individuals in the Skeletal Collection of the Croatian Academy of Sciences and Arts, Zagreb, and found only four cases of bone neoplasms, all from benign conditions *(Proc Eur Ass Ca Res 2004 277 Abs # 453)*.

Dr. Mario Slaus (Croatian Academy of Sciences and Arts, Zagreb) said there was no evidence of secondary bone tumours in any individual in the collection, ''a factor that is probably explained by the fact that the mean age-at-death of the specimens is 35.6 years.''

This finding contrasts with a review on *The treatment of cancer in Greek antiquity* (*EJC*, this issue), which details observations of malignant tumours from the Hippocratic corpus (460–370 BC) up to the 7th Century AD. Over this period (more than 1000 years), cancers were observed and described. Surgery was performed for breast cancer, for example, but discouraged for cancers of the head, neck and back.

Herbs, oil, vinegar and medicinal minerals appear in numerous instances in the remedial preparations. 'The same prescriptions – in essence – were transmitted from one medical collection to another, from Greek Antiquity and throughout the Middle Ages,' the authors conclude.

EUROFILE

Gene patents: a myriad of issues

The decision by the European Patent Office (EPO) on May 18, 2004, to revoke the patent held by Myriad Genetics Inc. on breast-cancer gene *BRCA1* has been welcomed by the European organisations that disagreed with its implementation. The Curie Institute (Paris, France) and the Gustave Roussy Institute (Villejiuf, France), two of the European organisations that filed an opposition, called the decision: ''a victory for all those whose conception of public health puts the principle of equal access to care before commercial interests''.

Despite the public opposition to the way Myriad (Salt Lake City, UT, USA) has used its *BRCA1* patents to gain exclusive rights on diagnostic tests for breast cancer, the EPO's decision further adds to the debate on whether gene patenting hinders medical research and delivery of healthcare.

The EPO awarded the *BRCA1* patent to Myriad in 2001 – 7 years after the company first filed for a US patent on *BRCA1.* Since the initial application for a US patent on *BRCA1* in 1994, Myriad has filed seven further patents on *BRCA1* in the USA to update the sequence. Investigations by the EPO found the first four patents related to inaccurate aminoacid sequences: only Myriad's fifth sequence filed in March, 1995, was correct. By this time, details of *BRCA1* had already been published and the sequence was no longer novel. As a result, the EPO withdrew the patent. Myriad has until the end of 2004 to appeal and further hearings are scheduled for January 2005, to review two more European patents filed by Myriad in 2001 on *BRCA1.*

In the patent revoked by the EPO, Myriad had ownership of the *BRCA1* gene and any product subsequently derived from use of the gene for therapeutic and diagnostic purposes – a situation allowing Myriad sole control over diagnostic testing for hereditary breast and ovarian cancer, requiring hospitals and laboratories to send clinical samples for testing to either Myriad or a licensed laboratory. Thus, European institutions analysing the protein by any method would have been in violation of the patent.

''What we have is a messy terrain of conflicting and overlapping patents'', says Bryn Williams-Jones (Faculty of Social and Political Sciences, University of Cambridge, UK). While European countries can use the *BRCA1* sequence unrestricted, Myriad still holds valid patents for *BRCA1* in the USA, Canada, and Australia. In these countries, questions are being asked about the effect this will have on provision

''WE HAVE A MESSY TERRAIN OF CONFLICTING AND OVERLAPPING PATENTS''

of genetic testing. ''Mv real concern is not about the clear cases where institutions are threatened with legal action if they use patented tests'', says Tina Piper (Intellectual Property Research Centre, University of Oxford, UK). ''Rather, it is about institutions that avoid administering those tests altogether because of fear of legal liability.''

There are wider concerns about the effects gene patenting will have on access to genetic testing within public and private health-care systems. Application of eligibility criteria for testing and genetic counselling in public health-care systems limits access to genetic testing to people regarded as high risk. Although patients might wait 6 months or longer for test results, this system is one way to control costs and thus access to care.

By contrast, companies such as Myriad apply fewer initial eligibility criteria for tests and only encourage people to seek genetic counselling by sending the test results to physicians – results that can be available within a matter of weeks. However, easier access could create a large demand for tests, adding to the health-care burden in some countries *(Community Genet* 2003; 6: 46–57). ''Privatised tests on the market may mean that inappropriate populations at low risk take tests and then make demands on pre- and post-test counselling that health-care systems have to absorb'', explains Piper.

Countries are now faced with the task of how to accommodate extra costs due to increased demand from private testing; or, in the absence of private testing, the task of providing reliable and coordinated testing facilities to support high-throughput analysis of high-penetrance genes like *BRCA1.*

In February 2004, Cancer Research UK obtained the European patent on *BRCA2;* an important acqusition for the charity, who wanted to keep the sequence accessible to all researchers and health-care workers. ''Getting a network of labs together is very important'', states Richard Sullivan (Head of Clinical Programmes, Cancer Research UK). ''If a patent is rejected, what happens in terms of delivering that test to patients across Europe? We need to ensure the *BRCA1* test is available through individual countries' heatlth-care delivery system, and that is up to national governments.''

At present, however, researchers and clinicians believe the patent system is too permissive. ''Despite some improvements'', says John Sulston (Sanger Centre, Cambridge, UK), ''current patenting practice in biology is still too broad''. Limitation of a pantentee's rights might help make gene patenting more acceptable in the medical

''RESEARCHERS BELIEVE THE PATENT SYSTEM IS TOO PERMISSIVE''

community *(Nature Rev Drug Discov* 2004; 3: 364–68). There are suggestions that basic work, such as gene sequencing, should not be patented to reinstate the distance between academia and industry; or between discovery and invention.

''Patenting a bit of DNA doesn't look anything like an invention. Is it a useful tool or is it only part of a puzzle?'' asks Williams-Jones. ''Patents have become such an accepted norm that if you don't have them you're out of the game''. For genes like *BRCA1,* the rules are set to continually change and, according to Sullivan, are ''yet another piece in the jigsaw on this broader debate of intellectual property for genetic sequences and the utility with which these sequences can be applied''.

Claire Tilstone

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Awareness medal for Czech registry

All doctors and nurses actively involved in the manual completion of Czech Cancer Registry records have been awarded a medal by the Czech Civic Association for Health Advancement and Cancer Prevention. The medal is intended to raise awareness of the role the cancer registry plays in the diagnosis, treatment and prevention of the disease.

Obligatory notification of cancer cases started in 1951 in the former Czechoslovakia. Registration criteria developed by the International Agency for Research on Cancer (IARC) have been applied since 1976. However, despite massive computerisation of the national registration system since 1992, the discipline of notification is waning. It is increasingly necessary to employ manual searches for patients or to complete missing information.

A further threat to the registry – as elsewhere in Europe – is the stringent legal framework relating to confidentiality. All information in the Czech Cancer registry is based on individual patient data and, since January 2001, the Coordinating Centre for Departmental Medical Information Systems in Prague has been responsible for the nationwide protection of patients' personal data. Access to personal data is a current political issue and the right of Czech cancer registers to record cancer patients' personal data is now being discussed by legislators.

The Czech Cancer Awareness Medal, designed by Dominika Charousová and Petra Hanzlíková

The medal, which is 50 mm in diameter and weighs 42 g, is made of silver and red brass. It carries the inscription: ''Evidence nádor, podpora jejich diagnostiky, terapie a prevence v esk Republice 2004'' (Cancer Registration – Advancement of Cancer Diagnosis, Therapy and Prevention in the Czech Republic, 2004). A total of 245 medals were presented in June 2004, the vast majority of which went to those involved in manual completion of the Registry records.

The medal was produced with the cooperation of the Czech Mint, the Arts Secondary School and the Specialist Secondary School in Jablonec nad Nisou. We hope it will be a lasting testimony to the Czech artistic skills as well as evidence of our efforts on behalf of health promotion.

Edvard Geryk
Board of Czech Cancer Registry,
Brno, Czech Republic

Screening 'prevented epidemic' of cervical cancer

The cervical cancer screening programme in Britain is preventing up to 5000 deaths a year from the disease, scientists say (*Lancet 2004;* ***364****: 249–56*). They estimate that the programme will prevent the premature deaths of about 100 000 women born between 1951 and 1970.

The study was set up against a background of reports suggesting that the reduction in mortality achieved by the UK national cervical screening programme is too small to justify its financial and psychosocial costs, except in a few high-risk women.

Cervical cancer mortality in England and Wales rose threefold from 1967 to 1987 in women younger than 35 years. By 1988, when the national screening programme was launched, incidence in this age range was among the highest in the world, despite substantial opportunistic screening. Since then, the rising trend has been reversed.

Professor Julian Peto (Institute of Cancer Research, London, UK) led the study for Cancer Research UK, and said the main reason for the rapid increase in cervical cancer death rate is presumably a long-term increase in the prevalence of human papillomavirus. Other factors – age at first intercourse, number of sexual partners, prevalence of other sexually transmitted diseases, and so on – could also be relevant.

The London/Cambridge based researchers used an age-cohort model and estimated that 1 in 80 British women avoid premature death by regular screening. A previous study (*BMJ 2003;* ***326****: 901*) put the risk at 1 in 1000. Reasons for the discrepancy include a difference in the cohorts studied: the *BMJ* study included women born between 1912 and 1950, whose underlying risk was much lower than those born after 1950. Further, the *Lancet* study assumed that opportunistic screening was preventing deaths before the national programme was set up.

''Despite occasional but widely publicised failures the British cervical screening programme is already remarkably successful and is still improving,'' Professor Peto concluded.

An accompanying editorial (*Lancet 2004;* ***364****: 224-6*) was more equivocal. Age-cohort modelling relies on historical disease-mortality trends and an estimated inflation factor. By contrast other, biologically based models depend on many variables, including incidence of HPV infection, transition rates between various disease states and so on.

''If, as Peto and colleagues conclude, the population effect of the national screening programme is indeed great, then screening for cervical cancer should continue – even though it is no longer a major public-health issue in the UK – until a vaccine against HPV or some other means of primary prevention becomes available,'' it states. ''However, if the screening programme is less successful, or the costs outweigh the benefits, funds for control of the disease might be more usefully directed elsewhere,'' it concludes.

PODIUM

The Lessons of History

Professor Michael Baum is Emeritus Professor of Surgery at University College London, having previously been Head of Breast Cancer Services at the Royal Marsden Hospital, London. He is a former President of the British Oncological Association and Vice-President of EUSOMA and was President of the European Breast Cancer Conference in March, 2004. He and Craig Henderson (UCSF, San Francisco) edited a collection of classic papers on breast cancer.

Professor Michael Baum

What did you learn from the experience?

Re-reading the original papers, I came across extraordinary misconceptions; the papers, particularly the older classics, are misquoted time and again. It is because we are all idle. Anyone quoting Beatson on the use of oophorectomy in breast cancer (*Lancet 1896*) quotes him from a book or paper they have just read. It is like Chinese whispers.

Why did Beatson's ideas lie dormant for such a long time?

Because it was far from clear why surgery on one part of the body should have an effect elsewhere. Hormones were not discovered for another 30 years. His observations had no rational explanation at the time, and were therefore dismissed. That is a continuing theme.

Was the scientific method intact 100 years ago?

The conventional belief is that laboratory research leads to animal work, and eventually into the clinic. But the opposite is true. Look at Beatson, or Huggins (*Cancer Research 1952*) who first described adrenalectomy: both were doing the right thing for the wrong reasons. Their work was based on empirical clinical observations and the science came later. It was not lab to clinic. It was clinic to lab to clinic.

Surely that would not be allowed now?

I insist the cycle continues. There are lots of inconsistencies in the behaviour of breast cancer, such as the hazard rate for relapse, which is not constant. It peaks 2–3 years after surgery, an observation which cannot be explained by conventional teaching. We told scientists that the act of surgery itself must do something to kick-start metastases. They then produced a slew of basic research which explains the clinical observations and suggests new lines of therapy – COX-2 inhibitors pre-operatively – which now need to be tried in the clinic.

How relevant is the historical perspective for today's practitioners?

To paraphrase George Santayana, if we do not learn from mistakes in the history of our subject, we are doomed to repeat them.

Why do paradigm shifts lead to progress?

You cannot explain the explosive advances of science as a linear process. What happens is that progress takes place within a hypothetical model but outlying facts – which do not fit – accumulate and a crisis is reached. The only way forward is to re-examine the conceptual framework, the limits to thinking. It is a painful process and usually the revolutionary scientists have to wait for the old guys to die, because the old guys simply cannot see it.

I lived through the shift from radical surgery to biological model of disease. The proponents of radical mastectomy believed that breast cancer had to be caught early and removed and would not consider the possibility that it had already spread by the time of diagnosis. They called us murderers, insane.

A shift is due in chemotherapy. Chemotherapists, who can only give higher doses or different schedules, cannot see that it does not work.

What would historic figures make of this?

Halsted, who described the radical mastectomy in 1894, said, 'Concepts from the past blind us to facts which slap us in the face'. It is true.

How far does personality determine the progress of a new idea?

Entirely. People need to be clever, have the courage of their convictions, and be prepared to dig in for the long haul. With electronic communication, virtual communities of like-minded people can support each other. It will be easier to challenge received wisdom and the pace of progress will accelerate.

How important is study of the scientific process?

It is essential. The scientific community is now sufficiently sophisticated to distinguish hypothesis from experimental data; government agencies are not. For example, women in the UK with suspected breast cancer must be seen within 2 weeks. This ought to be a good idea, but is not. It just means that those not thought to be urgent wait 6 weeks. Government agencies threaten scientific progress and doctors need to influence political decisions.

A number of the classic papers are relatively recent. Why is that?

We are living through historic times: the Human Genome Project, the unravelling of cytokine mechanisms, proof of principle of targeted therapy with Herceptin, the shift from morphological to molecular classification. The pace of discovery will accelerate, but there is a limit to the rate of progress, which is fixed by the natural history of breast cancer.

What patterns emerge from the book as a whole?

Almost every chapter starts with classic papers, which in the fullness of time have been shown to be wrong. Classics are defined by where they led, they are the papers which generated cascades of activity. That is why they deserve to be remembered.

'Classic Papers in Breast Disease', edited by Michael Baum and Craig Henderson, is published by Martin Dunitz, 2004. ISBN: 1 90186 583 5. See www.dunitz.co.uk