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INTRODUCTION



Dr Christopher Wild

THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER WAS ESTABLISHED AS THE SPECIALISED CANCER AGENCY OF THE WORLD HEALTH ORGANIZATION (WHO) BY A RESOLUTION OF THE WORLD HEALTH ASSEMBLY IN 1965. THE FOUNDATION OF ALL THAT THE AGENCY DOES IS ITS EXCELLENT REPUTATION FOR CONDUCTING THE HIGHEST-QUALITY INTERNATIONAL CANCER RESEARCH. OTHER ACTIVITIES, OF UNDOUBTED MAJOR IMPORTANCE, NEVERTHELESS FIND THEIR LEGITIMACY IN BEING PERFORMED IN THE CONTEXT OF AN ORGANISATION AT THE FOREFRONT OF RESEARCH IN ITS AREAS OF EXPERTISE. IN MY FIRST YEAR IN OFFICE I WOULD ALSO EMPHASISE THE TREMENDOUS SUPPORT AND GOODWILL EXPRESSED TOWARDS THE AGENCY BY THE INTERNATIONAL SCIENTIFIC COMMUNITY. SUCH SUPPORT IS MANIFEST IN TOO MANY WAYS TO DETAIL, BUT UNDOUBTEDLY IS A KEY CONTRIBUTOR TO THE SUCCESSES DOCUMENTED IN THIS REPORT.

The Agency's tasks are stated in its Statute, in which the guiding principle is to promote international collaboration in cancer research. Specifically, the Statute of IARC states its role as:

- Planning, promoting and developing research in all phases of the causation, treatment and prevention of cancer;
- Collection and dissemination of information on the epidemiology of cancer, on cancer research and on the causation and prevention of cancer throughout the world;
- Studies on the natural history of cancer; and
- Education and training of personnel for cancer research.

Given that the Statute remains largely unchanged after forty-five years it is remarkably well adapted to the cancer research needs of the future. It is also evident that the contribution to be made

by an international cancer research agency has never been greater. The burden of cancer is rising markedly worldwide, with estimates indicating that by 2050 there will be double the current number of around 12.5 million new cases per year. Strikingly, however, the majority of the increase is expected in low- and middle-income countries, where health services are least able to meet the impending challenge. If left un-addressed this rise in cancer cases will create enormous hardships at the economic, social and personal levels. The emphasis the Agency has placed on identifying the causes of cancer and also evaluating strategies for prevention, both primary and secondary, are a valid response to these challenges, particularly in areas of the world where the opportunities for curative treatment are currently limited.

Therefore the Agency must orientate its activities over the next two decades such that it can best contribute to combating the projected increase in the global cancer burden. It should make its contribution in a way that is consistent with its Statute, plays to its strengths as an international organisation and makes most effective use of its partnerships, nationally and internationally. At the core of its function remains the generation of evidence that, through the conduct of novel research, informs strategies for cancer prevention and control. There are a number of principles underpinning the priorities the Agency makes in addressing its mission.

First, as mentioned above, is the emphasis on research, thus distinguishing the Agency from other international cancer organisations that focus on developing policy and advocating change in order to implement cancer control. This distinction establishes the basis of the complementary relationship with the WHO, where the research conducted by the Agency (e.g. in cancer screening or vaccination) can be translated by WHO into plans for action. A strong working relationship is essential to the success of both organisations. Second is the effort to add value by participating in and promoting collaboration in research. Collaboration is increasingly important not only for scientific reasons—for example, where large multi-centre international studies are required in order to identify risk factors—but also to ensure efficiencies and economies of effort in times of limited resources. Third, since its inception the Agency has promoted interdisciplinary research, pioneering the integration of laboratory sciences and population-based research. This approach has never promised as much as in the current era, where a new understanding of the complexity of carcinogenicity combined with technological advances promises a level of refinement of measurement not previously available to epidemiology. Increased understanding of mechanisms and the associated technologies (for example, “omics”) provide a major opportunity for translational research from the laboratory to the population. Fourth, the Agency has a worldwide mandate including the opportunity to conduct and support research in areas of the world where resources are limited. It remains one of the great values of the Agency that

its now twenty-one Participating States share a common vision in relation to this international mandate. Fifth, the inclusion of education and training as one of the four highlighted aspects of the Agency’s mission is vital, providing as it does the opportunity to build a new generation of cancer researchers worldwide with the motivation and skills to tackle the growing global cancer burden mentioned earlier.

CORE ACTIVITIES

Based on these principles drawn from its Statute, the Agency has a number of core areas that are achieved through its scientific and support structures. These comprise the following:

1. Describing the global cancer burden. The Agency aims to be the definitive international point of reference for collection, storage and statistical analysis of accurate data on cancer prevalence, incidence, survival and mortality, including for childhood cancer through avenues such as GLOBOCAN and Cancer Incidence in Five Continents.

2. The IARC Monographs. The Monographs have an international reputation for evaluation of evidence regarding the causes of cancer through its Working Groups. Identification of risk factors is fundamental to cancer prevention, and the conclusions of the Monographs are used by national health agencies to develop approaches for preventing exposure to known and suspected carcinogens.

3. Cancer etiology. This comprises one of the largest areas of activity in the Agency, with contributions across the organisation. The environment (defined in its broadest sense to include lifestyle, nutrition and occupation in addition to physical, chemical and biological factors) plays a role in the overwhelming majority of cancers and consequently, at least in principle, offers opportunities for research to be translated to prevention.

4. Mechanisms of Carcinogenesis. An understanding of mechanisms makes a fundamental contribution to cancer prevention in a number of ways, notably through: providing plausibility to exposure-disease associations; providing biomarkers of exposure, susceptibility,

early detection and prognosis; and offering opportunities for evidence-based interventions to interrupt the carcinogenic process. This research provides the essential bridge from basic sciences to population-based research at IARC.

5. Cancer Prevention. Research into the effectiveness of intervention strategies is critical, including understanding how these can be best implemented at the population level in particular socio-economic and cultural environments. Increasingly this research requires skills in behavioural epidemiology and health services research.

6. Education and Training. The Agency will place more emphasis on developing an integrated and expanded programme of education and training. The activities will include the strengthening of the Fellowships and Courses Programmes with an expanded remit. In addition to supporting scientists from low- and medium-resource countries, the Agency will seek to expand support to young scientists from high-income countries to encourage people with a desire to devote a career to international cancer research.

SCIENTIFIC HIGHLIGHTS

The scientific achievements of the Agency are presented by Section in this biennial report. The exciting progress speaks highly of the quality and energy of all working at IARC. There are many highlights that could be selected; those presented below serve to illustrate major findings but also emphasise the validity of working to the principles outlined above in driving the directions of the Agency’s research and related activities.

During the biennium the Agency published the ninth volume of *Cancer Incidence in Five Continents*, with the print version being subject to careful revision before becoming available in 2009, following the web-based release of the volume in 2007. All eight previous volumes are available through the website as part of the *CANCERmondial*, which serves as a point of reference for information on cancer occurrence on an international scale. The Agency was also able to provide CanReg5 software as a support to cancer registries worldwide.

In another of the Agency's flagship projects, the IARC Monographs, the major task was undertaken of reviewing all Group 1 human carcinogens in six parts for Volume 100 of this series. The international Working Groups evaluated evidence that led to new conclusions establishing the links between hepatitis C virus and non-Hodgkin lymphoma, formaldehyde and leukaemia, and asbestos and ovarian cancer, among others.

In terms of how research at the Agency integrates laboratory and population-based research into etiology and prevention, the example of cervical cancer is a model one. There are over half a million new cases of this tumour worldwide each year, most occurring in low- and middle-resource countries. With the advent of HPV vaccines, both vaccination and "screen and treat" approaches can be considered to combat this cancer, and the Agency has made major contributions in both areas. Successful introduction of vaccines as well as screening with HPV-based testing requires knowledge of the infection burden and type-specific distribution of HPV types. The Infections and Cancer Epidemiology Group has provided novel data through its HPV surveys, and through this work has made the important observation that in some populations, high prevalence does not diminish with age. This information is critical in the development of prevention strategies. At the same time, the Infections and Cancer Biology Group has made exciting findings concerning the oncogenicity of different HPV types, both mucosal and cutaneous, particularly in relation to the establishment of chronic infection. A key protein involved in innate immunity, toll-like receptor 9, is down-regulated by HPV oncoproteins and this effect differs among HPV types, thus possibly explaining the heterogeneity in risk associated with the different HPV types.

In parallel to the above studies, Dr Sankaranarayanan and his collaborators in India showed in a cluster randomized trial that a single round of screening using HPV testing resulted in close to a 50% reduction in the numbers of advanced cancers and deaths from cervical cancer (Sankaranarayanan et al., 2009). This collaborative effort has significant public health importance in demonstrating the

value of different screening approaches in cervical cancer prevention in low- and middle-income countries. A new study of around 20 000 girls in eight centres in India has been initiated to compare two doses versus the standard three-dose HPV vaccination schedule in order to guide public health policies for vaccine implementation.

It is evident that a majority of human cancers have an etiology involving environmental risk factors played out on an individual genetic background of varying susceptibility. Consequently, the identification of genetic variants associated with risk is one way to help elucidate how environmental factors exert their effects. These studies require large numbers of subjects which in turn demand multi-centre international collaborations. The Agency has taken leadership in a number of areas and made major advances in identifying susceptibility loci for cancers of the lung, upper aerodigestive tract and kidney. Notable highlights were the reporting of genome-wide association studies that revealed two new susceptibility variants for lung cancer, 15q25, which contains three nicotinic acetylcholine receptor genes, and 5p15.33 (McKay et al., 2008). These observations involved external and internal collaboration with major contributions from the GEP, GCS and LCA Groups. The observations have also stimulated new research within the MOC Group on the functional effects of these variants, notably the 15q25 locus.

Improved methodology to conduct cancer research is also a feature of the Agency's activities. Areas of particular interest here include the progress made in developing the EPIC-Soft® tool as a standardised, computerised 24-hour recall programme applicable across different populations with markedly varying diets (Linseisen et al., 2009). In turn there are exciting initiatives developing biomarkers for epigenetic changes (Vassiere et al., 2009) complementing approaches to measure mutational events (Igetei et al., 2008), both methodologies being applicable to small volumes of blood available from prospective studies such as EPIC.

The Agency played a major role in a number of additional international collaborative studies and consortia, for

example on lymphoma (InterLymph), lung (ILCCO) and head and neck (INHANCE) cancers. The Agency also contributed to important emerging areas of concern, notably the growth in pediatric diagnostic procedures using X-rays and high-dose techniques (e.g. CT scans), through the Child-Med-Rad collaboration. In addition, the Agency took the lead in an important and unique international cooperative project called the Agenda for Research on Chernobyl Health (ARCH) which will set priorities for future investigations of this accident, including understanding the impact of low-dose radiation exposure on cancer risk.

Large-scale prospective studies are far less frequent in low and middle-resource countries than in high-resource countries. However, the Agency has made significant progress with a Russian cohort in Western Siberia and also a prospective study in Golestan province in Northeast Iran, where there are particularly high incidences of cancer of the stomach and oesophagus. In the Russian cohort a remarkable observation was the strong indication that more than half of deaths in males aged 15–54 were due to alcohol (Zaridze et al., 2009).

The Agency balanced its research on etiology with that on prevention. In addition to the work cited above on cervical cancer, there were major efforts in relation to tobacco. Notably this concerned publication of two Handbooks of Cancer Prevention (cited below), an example of the close cooperation developed with WHO and support to the implementation of the WHO FCTC. Agency scientists also provided leadership to development of European guidelines for quality assurance in cervical cancer screening, again an area of strong cooperation with WHO (Arbyn et al., 2008).

PUBLICATIONS

The Agency published a high volume of peer-reviewed scientific papers in top-quality journals in its fields of expertise as detailed in this report. It is noteworthy how many of the publications involve young scientists training at the Agency and also how many reflect the international collaborations that characterise much of the Agency's work.

The Agency is responsible for the *WHO Classification of Tumours* series, the so-called “Blue Books”, renowned worldwide for their quality. Production of the 4th Edition is currently in progress, and additional resources will be assigned to support future activity in this area. In this biennium the second volume was produced, entitled *Tumours of the Haematopoietic and Lymphoid Tissues*, and has demonstrated quite remarkable sales, with 22 000 copies sold to date in calendar year 2009.

Two Working Group reports came out during the biennium, one on Vitamin D and cancer and the other on the IARC Code of Good Scientific Practice. In

addition, there were two volumes of the *IARC Handbooks on Cancer Prevention* published, both of which were dedicated to different aspects of tobacco control, one entitled *Methods for Evaluating Tobacco Control Policies* (2008) and another on *Evaluating the Effectiveness of Smoke-free Policies* (2009).

EDUCATION AND TRAINING

The Agency has for many years awarded post-doctoral fellowships to young scientists to contribute to development of cancer research. In the last five years almost 50 fellowships have been awarded through this programme to scientists from low- and medium-resource

countries. During 2008–09 fellows came from Bulgaria, the People’s Republic of China, India, Indonesia, Mongolia, the Russian Federation and Thailand. The programme was successful in attracting an EU Marie Curie Action grant to increase the number of awards for next year. At the same time, the continued support of the Italian Association for Cancer Research is highly appreciated. It is important to point out that the award of fellowships from the Agency’s own programme comprises only a small fraction of the total contribution to post-doctoral training, with the Agency hosting between 80 and 100 trainees, masters/doctoral students, technical students, posts docs and visiting scientists each year. In 2009 the Agency also awarded two senior Visiting Scientist Awards to Professor Julian Peto (London, UK) and Professor David Richardson (Chapel Hill, North Carolina, USA).

The IARC courses are another route by which support is provided to cancer researchers worldwide. Over the biennium the IARC Summer School attracted 116 participants, many from low- and medium-resource countries, organised two cancer registration training courses in the People’s Republic of China and the Republic of Korea, and delivered six courses in cervical cancer screening and prevention in the People’s Republic of China, India, Tanzania, Gabon and Morocco. A feature of the IARC courses is that they are contiguous with our research programmes, and thus many of the participants are already or become active collaborators with Agency scientists.

MAJOR RESEARCH AWARDS

The Agency continues to successfully attract extrabudgetary resources through competitive grants from major funders. The Monograph programme is a case in point, which after a very high scientific score is well positioned to receive a prolongation of the long running, NCI-funded “Evaluation of Carcinogenic Risks to Humans” project, which should be extended for a further 5 years at a budget level of roughly USD 1 000 000 per year. Furthermore, competitive and direct funding was received this year from the American Cancer Society, the US Environmental Protection Agency and the NIEHS, totalling USD 230 000.



Figure 1. Christopher Wild with IARC Medal of Honour Recipients Harald zur Hausen

The groups in the Section of Nutrition and Metabolism continued to successfully receive funding from the World Cancer Research Fund (WCRF). In addition to 3 already active grants, IARC received two further grants as coordinator (together just under USD 500 000) and is currently negotiating a subaward as partner in a third award (USD 50 000). Also, a new funding opportunity was established by joining a consortium through a subcontract to be paid by the European Food Safety Agency (EFSA). The subcontract is currently being negotiated, and should fund our activities at a level of roughly USD 175 000.

Two major awards from the European Commission are currently in negotiation: Cagekid, a large 5-year collaborative project on kidney cancer genomics, which earmarks USD 1 600 000 of a total USD 17 500 000 for IARC's contribution; and CHANCES, a similar, large collaborative 5-year project with a similar overall budget and a share of USD 480 000 for IARC. The following grants were signed with the Commission in the last biennium: IARC Fellows, a project co-funding the IARC postdoctoral fellowships programme with a budget of USD 1 200 000 over 4 years; PPACTE, a small collaborative research project over 3 years that focuses on tax incentives to reduce tobacco consumption, with an IARC budget of USD 480 000; and a direct contract with the EC DG SANCO focussing on several projects, including the European Code Against Cancer and a European Cancer Atlas (budget USD 650 000).

The Agency has also continued to be competitive with French funders, with 5 awards from the INCA (30% success rate) and 8 projects funded from the Ligue Contre Le Cancer (66% success rate).

IARC MEDAL OF HONOUR

In 2008 the IARC Medals of Honour were awarded to Maurice Tubiana, member of the French Académie des Sciences and the French Académie de Médecine; Professor Jan Hoeijmakers, Head of the Department of Genetics, Erasmus Medical Centre; and Sir Richard Peto, Professor of Medical Statistics & Epidemiology at the University of Oxford.



Figure 1. ... and Nubia Munoz

In 2009 the Agency awarded the IARC Medal to two distinguished scientists for their truly exceptional achievements in cancer research, namely the identification of human papilloma virus (HPV) as a necessary cause of cervical cancer and the development of a dual strategy to reduce the burden of this cancer by vaccination and by screening. Professor Harald zur Hausen from the German Cancer Research Centre was awarded the Nobel Prize in Medicine in 2008 “for his discovery of human papilloma viruses causing cervical cancer”. Professor Nubia Muñoz made major contributions to the establishment of the etiology of cervical cancer through her pioneering epidemiological studies during her

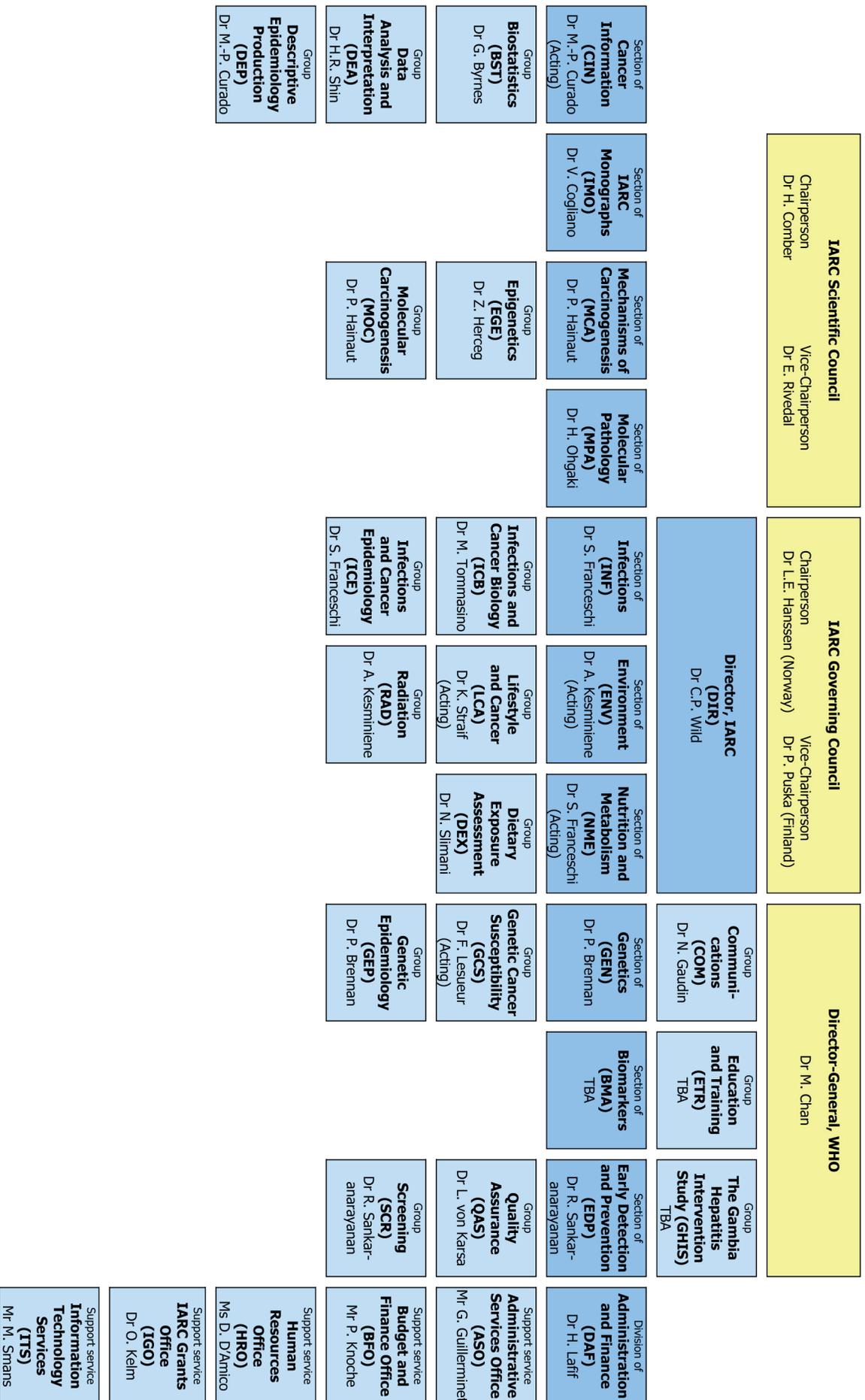
distinguished career as a scientist at IARC. It was a particular pleasure to welcome Nubia back to the Agency to receive this award (Figure 1), and her example of what can be achieved through the Agency is an inspiration to the next generation of young research scientists at IARC.

SCIENTIFIC ORGANIZATION

Dr Peter Boyle's term of office as Director of IARC came to an end in December 2008. Dr Boyle had a major impact on the Agency, not just in his time as Director but also previously as a staff scientist from 1986–1991. Aside from his scientific initiatives, Dr Boyle was notably

International Agency for Research on Cancer World Health Organization

1 December 2009



TBA: to be appointed

Figure 2

/mg

successful in encouraging the admission of several new Participating States to the Agency during his tenure. The publication of the World Cancer Report (2008) edited by Drs Boyle and Levin represented a major effort from many colleagues across the Agency.

The scientific organisation of IARC was changed during 2009 in order to align it with the future strategic directions and to provide clear leadership in key areas. The current structure comprises nine Sections, each with one or more research Groups. The Sections are: Cancer Information, IARC Monographs, Mechanisms of Carcinogenesis, Molecular Pathology, Infections, Environment, Nutrition and Metabolism, Genetics, and Early Detection and Prevention (Figure 2). These changes give increased emphasis to core areas such as cancer information (including cancer registration), the Monographs programme and early detection and prevention as well as providing renewed emphasis on nutrition. New senior appointments to support these initiatives for 2010 include Professor David Forman (formerly at the University of Leeds, UK and National Cancer Intelligence Network, UK) and Professor Isabel Romieu (formerly at the National Institute of Public Health, Mexico).

In order to support the scientific activity, two leadership committees were created. The first is the Senior Leadership Team (SLT), comprising the Director, all Heads of Sections, the Director of Administration and Finance (DAF) and the Head of Communications. The primary role of the SLT is to provide strategic leadership to the Agency through its advice to the Director. The second leadership committee is the IARC Operational Team (IOT), comprising the Director of Administration and Finance, the Heads of the Support Services (Finance, Human Resources, Buildings, Information Technology, Grants, Communication), and one Section Head. The primary role of the IOT is to ensure the support services enhance the scientific activity of the Agency.

PARTICIPATING STATES

During the biennium a further participating State, Austria, was admitted to the

Agency, bringing the total number to twenty-one. In October 2009 the Agency held a one-day workshop in Vienna in cooperation with the Austrian Federal Ministry of Science and Research which was attended by around 100 participants from across the country together with six staff from the Agency.

DIDIER COLIN

It was with great sadness that Agency staff learned of the untimely death of our colleague Didier Colin in November 2009 at the age of 43 years. Didier worked at the Agency since 1992, beginning in the Environmental Cancer Epidemiology Unit and since 2003 working in Infections and Epidemiology Group. Didier was a committed, professional staff member, discreet and determined. He was also a warm friend to many and will be sadly missed by all. The Agency extends its condolences to the family and friends of Didier.



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IARC MEDALS OF HONOUR



ROGER SOHIER LECTURE

- 1993 Gérard Orth (Institut Pasteur, Paris) – Papilloma virus and human cancer
- 1994 Guy Blaudin de Thé (Institut Pasteur, Paris) – Epidémiologie moléculaire des rétrovirus oncogènes
- 1995 Richard Peto (Oxford University, UK) – Avoidance of premature death
- 1996 Dirk Bootsma (Erasmus University, Rotterdam, Netherlands) – DNA repair: maintaining nature's perfection
- 1997 Luca Cavalli-Sforza (Stanford University, CA, USA) – Gènes, peuples, langues, cultures
- 1998 Charles Weissmann (University of Zurich, Switzerland) – Biology and transmission of prion diseases
- 1999 Jan Pontén (Uppsala University, Sweden) – Sunlight and skin cancer: New insights
- 2000 Richard Klausner (National Cancer Institute, Bethesda, USA) – The war on cancer: Where we are and where research is taking us
- 2001 Oliver Brüstle (Institut für Neuropathologie, University of Bonn, Germany) – Embryonic stem cells: Basic concepts and therapeutic applications
- 2002 Jeffrey Koplan (Centers for Disease Control, Atlanta, USA) – Bioterrorism and public health preparedness
- 2003 Paul Kleihues (Director, IARC) – Poverty, affluence and the global burden of cancer
- 2004 Umberto Veronesi (European Institute of Oncology, Milan, Italy) – Breast cancer management and care: Current results and future perspectives
- 2005 David Lane (University of Dundee, UK) – p53 and human cancer: The next 25 years
- 2006 Georg Klein (Karolinska Institute, Sweden) – Viral contributions to tumorigenesis
- 2007 Mariano Barbacid (Centro Nacional de Investigaciones Oncológicas, Spain) – Ras genes, Ras oncogenes and cancer
- 2008 Jan Hoeijmakers (Rotterdam, The Netherlands) – Genome maintenance and the link with cancer and ageing
- 2009 Harald zur Hausen (German Cancer Research Centre, Heidelberg) – The search for infectious agents in human cancers

RICHARD DOLL LECTURE

- 2004 Richard Doll (London, UK) – Fifty years follow-up of British doctors
- 2005 Brian MacMahon (Needham, MA, USA) – Epidemiology and the causes of breast cancer
- 2006 Joseph Fraumeni Jr (National Institutes of Health, USA) – Genes and the Environment in Cancer Causation: An Epidemiologic Perspective
- 2007 Dimitrios Trichopoulos (Harvard School of Public Health, USA) – Breast cancer: Epidemiology and etiology
- 2008 Sir Richard Peto (Oxford, United Kingdom) – Halving premature death
- 2009 Nubia Muñoz (National Cancer Institute of Colombia) – From aetiology to prevention: The case of cervical cancer



IARC LECTURE

- 2005 Tadao Kakizoe (National Cancer Centre, Tokyo, Japan) – Bladder cancer: A model of human cancer determined by environmental factors and genetics
- 2006 Ketayun Dinshaw (Tata Memorial Hospital, India) – Cancer Treatment and Control
- 2007 LaSalle D. Leffall on behalf of Ambassador Nancy G. Brinker (Komen Foundation, USA)
- 2008 Maurice Tubiana (Paris, France) – La prévention des cancers, de l'analyse scientifique des données à la prise en compte des facteurs psychosociologiques