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European Journal of Cancer 38 (2002) S14–S18

European Journal of Cancer

www.ejconline.com

The EORTC Laboratory Research Division

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Abstract

The Laboratory Research Division (LRD) of the EORTC currently consists of five Groups with expertise that includes preclinical drug development, all aspects of cancer pharmacology, clinically-relevant receptor and biomarker studies, functional imaging and contemporary pathology. The LRD provides a Europewide resource for cancer clinical trials with particular expertise in the evolving field of translational research. In the development of therapies designed to exploit the molecular and cellular pathology of cancer, it is essential that translational research is included at all stages and the EORTC, through the LRD, has access to such expertise. In addition to providing support for drug development and clinical trials, the LRD represents a unique forum for the development of contemporary translational research expertise, the establishment of quality standards and the education of young laboratory and clinical scientists embarking on careers in oncology.

Keywords: Drug development; Pharmacology; Biomarkers; Functional imaging; Pathology

1. Introduction and highlights

The Laboratory Research Division (LRD) of the EORTC exists to enhance translational research conducted as part of EORTC clinical trials. Translational research encompasses:

- the identification of new therapies in preclinical studies,
- the evaluation of novel drugs in mechanistic clinical trials (using contemporary pharmacokinetic, pharmacodynamics and functional imaging approaches) and
- the conduct of molecular (direct and surrogate marker) and cellular pathological studies, and functional imaging, in conjunction with phase II and phase III investigations.

Within the LRD, there are five Research Groups and each of these is a unique European resource comprised of a network of experts and laboratories with many years' experience in their chosen field. Consistent with the changes in clinical and laboratory research that have taken place over the last 40 years, LRD Groups have formed, merged and re-focused in response to important scientific and technological advances. The LRD has been a major force in the implementation of a number of important developments [1–12] and these include:

- Contemporary *in vivo* tumour model systems (Screening and Pharmacology Group).
- Pharmacologically-guided dose escalation and population pharmacokinetic studies (Pharmacology and Molecular Mechanisms Group).
- Steroid receptor and, more recently, high throughput genomic biomarker assays (Receptor and Biomarker Study Group).

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0959-8049/02/$ - see front matter
PII: S0959-8049(01)00455-5

- Positron emission tomography (Functional Imaging Group).
- Virtual (electronic) tissue banks and pathological review (Pathology Group).

The above areas are all at the forefront of contemporary translational research and the EORTC LRD has played a major role in fostering these approaches in association with drug development and clinical trials. The strengths and achievements of the LRD as it stands today are largely a reflection of the vision of former LRD Chairmen (notably Professor Tom Connors) and the enthusiastic commitment of the individual Group members and the Group officers. The meetings of the Groups and inter-LRD Group meetings are characterised by a spirit of collaboration and camaraderie that is as important to successful research as the resources available for the studies.

Recent developments in the treatment of cancer, notably the identification of trastuzumab and imatinib as agents with significant and selective activity, emphasise the importance of target-based drug discovery and mechanistic early clinical trials. Through the LRD, the EORTC has access to the expertise and experience needed for target-based drug discovery and development, thereby ensuring that the EORTC will remain a competitive clinical trials organisation.

2. Screening and Pharmacology Group (SPG)

One of the strengths of the EORTC LRD has always been a preclinical screening programme for potential anticancer agents. In 1972, the Experimental Screening Group merged with the Preclinical Pharmacology Group to form the Screening and Pharmacology Group (SPG). The SPG is one of the longest standing EORTC Groups.

The main objective of the SPG is to evaluate potential anticancer drugs and to provide antitumour and toxicity testing systems to investigate new agents, and to study their mode of action, toxicity and other pharmacological properties. In this way, the Group alerts the EORTC Clinical Groups to new agents that are potentially interesting in the treatment of cancer. The SPG has members, currently 35, in many of the major cancer research institutes in Europe, and contributes to many aspects of new drug development, such as synthesis, primary screening, secondary evaluation, mode of action, toxicology, etc.

To maintain confidentiality when considering unpatented compounds, the SPG meets in closed sessions. Membership is by invitation only and is maintained by active contribution. The membership is a balance of chemists, biologists and clinicians with an interest in drug development. The close collaboration of chemists and biologists facilitates structure/activity studies and analogue development to ensure that only agents with a real potential for anticancer activity are progressed to clinical trial.

The Group meets twice a year to present and discuss new screening results and business meetings are typically round-table discussions on chemistry, screening results, pharmacology and toxicology of a range of different compounds developed in each member's own institution, or elsewhere. Ultimately, the SPG produces dossiers on new drugs for submission to the EORTC New Treatment Committee for consideration for clinical trial. Between 1982 and 1997, seven such dossiers were produced by the Group and, in recent years, members of SPG have been involved in the preclinical evaluation of agents such as: Flavone acetic acid, EO9, AQ4N, imidazoacridinone C-1311, and Phortress (NSC 710305). In addition to business meetings, the group has organised eight workshops on specific themes. These have a more open character and generally involve members from other EORTC Groups. Furthermore, the SPG conducts 'mini-projects', linking the expertise of individuals from several centres in Europe. Since 1985, 17 such projects have been supported.

In 1993, the EORTC LRD established a joint venture with the Cancer Research Campaign (CRC, UK) and National Cancer Institute (NCI, USA) to develop a pharmacological approach to the development of new anticancer agents identified by cell line screening at the NCI, and the SPG has played a major role in this initiative. The process starts with the review of the available NCI data of European compounds by a panel of CRC/EORTC members. Compounds are selected on the basis of the COMPARE analysis, mean graph and growth curve profiles, potency, molecular target data and novelty of chemical structure. The selected compounds then undergo systematic development according to Standard Operating Procedures. Compounds are subjected to preformulation, assay development and stability studies. If the compound can be formulated, the maximum tolerated dose (MTD) in mice is determined using single-dose intraperitoneal (i.p.) administration, followed by plasma pharmacokinetics at various time points using the MTD. If the plasma concentrations approach *in vitro* IC_{50} values obtained in the NCI *in vitro* cell line screen, the compounds qualify for further *in vitro*/*in vivo* antitumour studies. Further mechanism-based testing procedures are currently being developed, for example for potential inhibitors of protein kinases and tubulin binders.

Since November 1993, approximately 1100 compounds have been reviewed by the CRC/EORTC panel as part of the above initiative, from which 50 compounds were selected. Since their selection, 26 compounds have been dropped: 20 for reasons of solubility, impurity, instability *or* insufficient bio-availability, 2 for

insufficient activity in human tumour xenograft models *in vivo* and 4 on other grounds. One compound has been shown to have significant activity and is undergoing further evaluation, and other compounds are at various stages of testing. The investigations on new drugs in EORTC are strongly supported by the National Cancer Institute (USA) through the invaluable help of Dr Omar Yoder and Dr Susanne Radtke of the NCI Liaison Office (Brussels), and Dr Edward Sausville and colleagues in the Developmental Therapeutics Programme (Washington, USA).

3. EORTC Pharmacology and Molecular Mechanisms (PAMM) Group

The PAMM Group, formerly the Pharmacokinetics and Metabolism Group, was formed as a sub-Group of the, then, EORTC Early Clinical Trials Group in the 1970s. The formation of the PAMM Group was stimulated by the recognition of the importance of pharmacokinetic determinants of drug action, as well as technological advances which made widespread pharmacokinetic studies feasible for the first time. The PAMM Group comprises basic and clinical pharmacologists, whose interests span the full breadth of cancer pharmacology, i.e.:

- tumour biology (*in vivo,* cellular and molecular),
- the development of new agents and new pharmacological principles,
- clinical pharmacokinetics and pharmacodynamics,
- anticancer drug bio-transformation, and
- mechanisms of drug resistance.

Combined input from both basic and clinical scientists in the same Group is a key feature of the Group, and allows the Group to achieve its goals. The Group is involved in the planning and conduct of clinical trials, both in members' own clinical institutions and in collaboration with the EORTC Early Clinical Studies Group. Increasingly, Group members are developing expertise in the area of surrogate markers and pharmacodynamic endpoints for early clinical trials, especially with respect to non-classical 'targeted' anticancer agents. A major objective of the PAMM Group is to stimulate research in Europe on the pharmacology, pharmacokinetics and molecular mechanisms of novel anticancer agents, and drug-related molecular pathology. The Group, which has about 300 active members, supports interaction between basic scientists and clinicians and fosters translational research with a pharmacological and molecular rationale. The Group's cohesion is maintained by popular and lively annual meetings (recently in Nancy, 1998, Amsterdam, 1999, Leicester, 2000 and Verona, 2001) organised jointly with EORTC LRD sister groups such as the SPG, which are attended by 100–150 delegates. These meetings constitute unique assemblies of European cancer pharmacologists and provide *fora* for fruitful discussion with international experts on topics pertinent to the latest methodologies, such as DNA microarray and proteomics, and novel concepts in anticancer drug design and development. The meetings constitute platforms for smaller quality-driven and demand-led workshops with specific scientific, clinical and industrial relevance. For example, the PAMM Group 'spear-headed' the implementation of pharmacologically-guided dosing escalation in phase I trials in Europe, and the introduction of broad-based pharmacokinetic monitoring in phase II trials, following successful workshops in Edinburgh and Glasgow, respectively. The group currently coordinates a European Union (EU)-funded clinical pharmacokinetic and pharmacodynamic validation study as part of selected EORTC clinical protocols, and also develops and validates new approaches to the clinical evaluation of tumour chemosensitivity.

In addition to promoting high quality clinical and laboratory science, the Group's meetings address an educational mission by encouraging scientific presentations from young European cancer researchers in front of a critical, but friendly, audience comprised of basic and clinical scientists. Highly qualified young investigators can obtain travel grants from the Group to permit attendance at PAMM meetings and to visit PAMM Group laboratories for the acquisition of new techniques.

4. Receptor and Biomarker Group (RBG)

The RBG started in 1972 as a 'spin off' of the Breast Cancer Group of the EORTC, with the remit of standardising the use of oestrogen receptor assays in early clinical trials of anti-oestrogens as an adjuvant treatment modality. With the increased use of anti-oestrogen-based treatments, more members, both biologists and clinicians from all over Europe, joined the 'Receptor Study Group'. Around the core activity of a Europeanwide quality control study for steroid receptor assays, the members generously shared, in a remarkably friendly and open atmosphere, their expertise and resources in the rapidly developing field of tumour biology. The most significant contribution of the RBG has been its 30-year-long organisation of quality control of steroid receptor assays, not only for EORTC institutions, but also for more than hundred laboratories in Europe and other countries.

In 1998, the group became the 'Receptor and Biomarker Study Group' in order to evaluate other biological markers with clinical relevance, e.g. proliferation markers, proteases and drug-metabolising enzymes.

Specific expertise in the collection, storage and assay of fresh and frozen tissues is a core competency of the Group, which has laid the foundation for many retrospective and several prospective studies of biological markers in cancer. The Group is now active in investigating various tumour types, such as breast cancer, brain tumours, colorectal cancer and prostate cancer. Furthermore, the identification and evaluation of potential predictive markers of treatment outcome has become a major focus for the Group.

It is already clear that an improved knowledge of tumour biology will become an integral part of cancer management in the clinic. Individually optimised treatment will lead to personalised medicine and a major challenge for all clinical trials organisations, including the EORTC, is to succeed in integrating both tumour biology and targeted therapy into clinical studies, starting at an early stage of protocol design and with appropriate technical support. As an example of this approach, and building on experience gained in the analysis of steroid receptors, the RBG has recently organised quality control studies of uPA and PAI-1 in prospective clinical trials, both as risk factors and markers of therapy response. A pooled analysis and a meta-analysis on the prognostic value of uPA and PAI-1 in patients with primary breast cancer has been performed which provides evidence of the clinical relevance of these biological markers in primary breast cancer. Studies are underway in order to demonstrate that a cost-effective combination of tumour biological parameters such as uPA and PAI-1 will complement or even replace more general and often subjective clinical decision-making factors. These 'clinical' target-identification and validation studies with uPA and PAI-1 are seen as a paradigm for future EORTC studies in which laboratory studies on clinical material will be used to support the development of drugs directed at defined targets.

5. The EORTC Functional Imaging Group (FIG)

The EORTC FIG was formed in 2000 from the EORTC PET Study Group, which was created in 1994. The aim of the Group is to unite European researchers in the functional imaging field with oncology drug developers, at both the clinical and preclinical levels. The last 15 years have been a period of exponential growth in methodologies for functional imaging. The ability to investigate hitherto 'invisible' processes has provided an unprecedented opportunity for oncology drug development. At the same time, it has not always been clear which imaging methodologies may be most relevant to specific clinical and preclinical research questions. There was therefore a clear need for a forum for interested functional imagers and oncologists. This need was particularly evident in the field of PET, and led in 1994 to the formation of an EORTC PET Study Group. The success of this initiative and the recognition of equivalent needs in functional Magnetic Resonance Imaging (MRI) and magnetic spectroscopy led to the creation of the 'tripartite' EORTC FIG in 2000.

Particular achievements of the EORTC FIG to date include:

- Recruitment of functional imaging specialists and oncologists from 44 centres in 14 countries within Europe.
- Correspondence, consultation and collaboration with institutions of higher learning, health services, and industrial concerns on a European and international level, focusing on the use of functional imaging technologies for patient care and anticancer drug development.
- Publication of EORTC guidelines for the use of FDG-PET in assessing response to therapy.
- Initiation and execution of the first clinical trial paralleling FDG with a phase I EORTC study to assess the utility of FDG-PET in detecting subclinical response to chemotherapy, and projects linking functional imaging technologies with other ongoing EORTC clinical trials.

Current initiatives are the development of a website to include a comprehensive on-line database on the use of FDG-PET to assess response to therapy (http://www.eortc.be/Groups/agroup.asp?gr=49&SH=PET), and a common strategy for the expansion of functional imaging technology within Europe, subject to discussions at the next annual group meeting in March 2002 in Heidelberg.

6. Pathology Group

The EORTC Pathology Group seeks to increase the involvement of pathologists in the EORTC Clinical Research Division disease-orientated groups in translational research. Translational research depends on the availability of tumour material, and as part of a project funded in 2000 by the Parthenon Trust, central support for histology review and banking of paraffin-embedded tissues in the EORTC is being developed. This initiative builds on previous projects like EUROPATH and the CANTOR project (Converging Agreement by Network Telematic for Object Recognition), a European Community 4th Framework initiative. Recently, a project was submitted in the context of the 5th Framework to broaden the scope of this research to frozen tissues. A key element in the tissue banking projects is the use of a virtual tumour bank to facilitate access to the available specimens across Europe. An essential aspect is the

input from health jurists to develop a generally accepted code of conduct on the use of human tissue, that is surplus to direct clinical needs, for biomedical research. The Pathology Group is also actively developing telematics as a key tool for pathological review by all EORTC Groups. Collaborations have already been established with the Melanoma, Soft Tissue and Bone Sarcoma, Genito-Urinary, Breast, Gynaecology and Lung Cancer Groups, and future studies are planned.

The Pathology Group is central to the translational research aspirations of the EORTC. Specifically, pathology studies are essential for target identification, clinical target validation, early- and late-stage clinical trials evaluation, and patient stratification on the basis of cellular and molecular pathological indices. The full integration of pathological studies into contemporary clinical trials will only be possible through the use of telematic approaches, and the Pathology Group is at the forefront of this evolving field.

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