The Alumni Club Symposium

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Help your reviewer review your cancer grant

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Many opportunities for support of cancer research for young investigators are currently available in Europe. New innovations encompassing all the aspects of basic cancer research, translational and clinical research are offered.

Although most resources of research support remain at the national level, several cancer grants are now offered by the different European Cancer Societies and organisms: FECS, ESMO, ESTRO, ESSO, EACR, EONS, SIOP, EORTC, UICC, European Cancer Leagues, European Commissions. Access through the web is open to everyone.

Key elements and review standards of a successful clinical, translational and basic cancer grant are the same.

- Does the project address an important problem in the field?
- Are the conceptual framework, design and methods, endpoints appropriate to the aims of the project and well justified?
- Are the aims original and innovative?
- Is the investigator appropriately trained and well suited to carry out the work?
- Does the scientific environment in which the work will be done contribute to the probability of success?
- Is the experience in recruitment of subjects well documented?
- Is your budget justified (over justified) in sufficient details to ensure a perception of competence?

Wrong answers to those questions make a reviewer annoyed and could easily explain why your application is not funded. A proactive approach is recommended.

And remind, if in God we trust, all others must bring data to support their grant.

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Practical evaluation of drugs developed to target specific molecular abnormalities in cancer

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In recent years, the development of anticancer agents has shifted emphasis from truely cytotoxic principles. Agents that either interfere with cellular communication processes or exploit the increasing knowledge of molecular variations of target molecules thought to be specific for cancer have increasingly attracted attention. Like with established agents, molecular target specificity remains an issues of importance for these new compounds which carry the promise to broaden the armamentarium of clinical therapeutics. New classes of agents include among others matrixmetalloproteinase Inhibitors, tyrosine kinase inhibitors, antiangiogenic compounds, compounds interfering with oncogene expression or activation (eg farnesyltransferase inhibitors). The exact differentiation between these groups sometimes may be blurry. Examples for molecular target abnormalities thought to be specific for malignancy include: c-erbB2, p53 mutations, and bcr-abl. - The development of primarily non-cytotoxic compounds challenges traditional endpoints in Phase I and Phase II trial designs as well as patient selection considerations in Phase III. In Phase I, the assumption of a co-linearity of clinical toxicity and efficacy is challenged. This mandates the inclusion of a measurement for target inhibition besides toxicity measurements which regularly poses issues concerning the validation of outcomes. The practicability of measuring target inhibition and its integration into the concept of dose-limiting toxicities and maximum tolerated dose will be discussed. In Phase II, the traditional watershed for product decisions, the usual endpoint of clinical tumor response is challenged since some of the newer generation agents are not designed to directly cause tumor cell death and subsequent tumor shrinkage. The design of Phase II studies will require adjustments and the issue of combination Phase II studies as guidance for further clinical development needs careful consideration. Also, randomized Phase II study designs might be helpful although clinical experience of this trial design is not frequently used for early anticancer drug development. In addition to Phase I and Phase II trial designs, Phase III pivotal studies will also have to undergo careful methodologic reevaluation. In summary, the identification of new targets and new target abnormalities has opened the opportunity to broaden concepts of trial methodology and most likely will provide us with clinically promising agents.

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Prevention of lung cancer in the new millennium

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In the UK, lung cancer is the most common malignancy and in Merseyside the cumulative rates for 1995, (0-74 years) are 11.7% for males and 7.3% for females, which are amongst the highest in the country. We have set up a population based study called 'The Liverpool Lung Project', which has two components. (i) A case-control study of newly diagnosed cases of lung cancer, which will provide a baseline risk assessment. (ii) A ten year prospective cohort study with a nested case-control design, which will identify markers of pre-clinical carcinogenesis.

The LLP studies will provide adequate statistical power to study the interaction between lifestyle and genetic susceptibility. Two specialist clinics, one mobile, has been set up to recruit individuals into the LLP using a dedicated team of nurses and interviewers. Detailed life style questionnaires as well as induced sputum and blood samples are taken and the recruits are invited back yearly, for 10 years. Underlying genetic susceptibility may, in part, be responsible for the high incidence of lung cancer in Liverpool. Interviews are carried out by trained interviewers using structured and semi-structured questionnaires, which cover tobacco consumption, medical history, diet, residential history, occupational exposures and family history.

We are using a range of technologies (i.e. genetic instability, mutation and expression profiling), to identify specific markers of lung cancer in sputum and bronchial lavage specimens. We have chosen well-documented markers and our aim is to test them in a pre-diagnostic clinical study, on automated platforms. Validation of certain biomarkers has been undertaken in tumour, bronchial lavage and/or sputum specimens. The importance of developing robust automated systems is a necessity for population based studies, such as this. We have undertaken this for genomic instability, which has been assessed for sensitivity and the limitations of high throughput fluorescent microsatellite analysis, for the detection of allelic imbalance. Chemoprevention has to be recognised a future clinical option and now is the time to develop the chemopreventive strategies in tandem with the developments in molecular genetic early detection techniques.

Supported by the Roy Castle Lung Cancer Foundation UK.