Also in families with exact the same mutation differences in pentrance and expression can be observed. In Leiden a large founder population is present showing a specific 19 basepair deletion called P16-Leiden and even these families show variation in nevus phenotypes and the association with pancreatic carcinoma. In part these variations may be explained by the presence or absene of risk modifying genes like genes for skin type, hair color, sun sensitivity etcetera. Also the presence or absence of genes involved in the formation of moles ("nevus genes" are not yet identified) may interact with the final phenotype of the patiënt. We have observed that P16- Leiden negative family members may show increased numbers of AN, indicative of nevus genes segregating in the family apart from the P16- Leiden mutation.
These observations of variable phenotype and uncertain cancer risks (and the very low yield of mutations in 2 case families) has lead to the opinion of the International Melanoma Consortium not to recommend DNA testing to patients and families.
Since the penetrance figures for the P16-Leiden mutation are fairly well known we have decided to start offering DNA testing to these families in a research setting. Non-mutation carriers are kept in the yearly skin screening if they exhibit 5 or more AN. Psychological studies are being carried out to study the impact of knowledge of gene carriers about their increased pancreatic cancer risk, a disorder for which no screening is possible and no preventive messures are known.

148 INVITED

Genetic predisposition in Spain and Latin America

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Introduction: The Genetics of Melanoma network is a non-profit international consortium (GenoMEL) focused in studies of melanoma genetic susceptibility in Europe, Australia, North America and Israel. Nowadays GenoMEL is obtaining samples and data from an even wider geographical and ethnical spread of familial melanoma in Latin America.
Objective: To study the well-known genes for melanoma (MM) susceptibility (CDKN2A/p14arf, CDK4, MC1R) in familial and multiple primary MM in Spain and Latin America.
Material and Methods: Patients with genetic susceptibility for MM (familial and multiple primaries) from Spain and Latin American countries and Sporadic melanoma cases from Spain were included. Genetic studies, clinical fenotyping and specific follow-up of a subgroup of patients are performed.
Results: CDKN2A mutations were identified in 30% of families, 10% of multiple primaries and 1% of sporadic cases. CDKN2A mutations are responsible of MM susceptibility in a substantial percentage of familial MM patients in Latin American countries. Some CDKN2A mutations have a founder effect: G101W or 358delG originated in Mediterranean countries and −34G>T originated in United Kingdom, some of them were detected in Latin American families. Other CDKN2A missense mutations were detected in Mexican families like I49T described in North America and M52T not previously described. One melanoma patient was homozygote for the I49T mutation in Mexico. The nonsense germline E88X CDKN2A mutation was detected in two not related Uruguayan families. MC1R gene modifies the penetrance of CDKN2A in Spanish population. In multiple primaries the risk to be carrier of a CDKN2A mutation increases with number of primaries, early age of onset and presence of familial history of melanoma. In sporadic melanomas, CDKN2A mutations were associated with gender (males), early age of onset and multiple primary melanomas. An specific follow up programme including total body photography, dermoscopy and recently confocal microscopy permits the diagnosis of early melanomas in high risk patients.
Conclusion: Knowledge on the genetic epidemiology and surveillance programmes of melanoma is of great interest and will contribute for an efficient and reliable management of high risk melanoma patients in Spain and Latin American countries.

Symposium (Wed, 26 Sep, 14:45−16:45)
The challenge of treating advanced pancreatic cancer from translational to clinical trials

149 INVITED

Are there rational novel targets for pancreatic cancer therapeutics? Observations from the M.D. Anderson Cancer Center SPORE in Pancreatic Cancer

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The recent failure of two large randomized phase III trials of the targeted monocloncal antibodies bevacizumab and cetuximab and the limited value of erlotinib has emphasized that therapy for advanced pancreatic cancer remains suboptimal. For this disease it now appears that therapeutically targeting individual proteins involved in the growth of pancreatic cancer cells will only lead to minor incremental improvements in patient survival. What should be our collective response to this fact? The pancreatic cancer SPORE at the M. D. Anderson Cancer Center is attempting to exploit aspects of pancreatic cancer molecular biology in order to discover and evaluate new targets for therapeutic development. Three general approaches are being taken: (1) Understanding the molecular biology of transcription factors activated pancreatic cancer and developing means to inhibit them. Thus far, we have analyzed NFκB and Specificity (Sp) proteins. NFκB has been targeted using the natural product curcumin with promising early activity documented in a pilot clinical trial. Sp proteins regulate many downstream proteins critical to cancer development and growth, including vascular endothelial growth factor. Non-steroidal anti-inflammatory agents such as celecoxib and tolfenamic acid promote proteasomal degradation of Sp1, Sp3, and Sp4 and will be assessed in future clinical trials. (2) Pancreatic cancer cells appear to be particularly susceptible to endoplasmic reticular (ER) stress and cellular proteotoxicity. ER stress can be induced in pancreatic cancer cells using the FDA-approved agent bortezomib. The proteotoxicity of bortezomib against pancreatic cancer cells appears to be due to the failure of bortezomib to stimulate the phosphorylation of PERK, leading to hypophosphorylation of eif2a. Despite bortezomib's inhibition of protein degradation through inhibition of the proteosome, eif2a allows protein translation to continue leading to cellular proteotoxicity. Combinations of bortezomib and protein disrupting agents such as SAHA or specific HDAC inhibitors appear particularly effective in stimulating apoptosis in pancreatic cancer cell lines in vitro and in vivo. A clinical trial assessing this therapeutic approach is underway. (3) Finally, new targets for pancreatic cancer are needed. We are therefore using a novel synthetic lethal screen in Drosophila to identify new targets that will then be evaluated and exploited in vertebrate systems. It is our belief that our efforts to develop new treatments for pancreatic cancer need to be closely integrated with the global efforts to understand the molecular biology of this disease and that future strategies should be rationally designed rather than empiric.

150 INVITED

Trial design issues in advanced pancreatic cancer

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Background: Progress has been slow in pancreatic cancer treatment. Although tumour biology is likely most important for this, design issues may contribute.
Methods: Reports of clinical phase II and III trials in major oncology journals during the past 10 years were scrutinized for aspects that could have influenced the treatment results. Some of these aspects will be discussed.
Results: The results of the many phase II trials, particularly in the locally advanced cases, are often more dependant upon patient selection than treatment efficacy. Since the gains in chiefly survival have been limited, the problems with sufficient power were of concerns, although lately several adequately powered phase III trials have been concluded. It could then be discussed whether some of the gains, shown to be statistically significant, are clinically meaningful considering toxicity and costs. It has been discussed whether patients with locally advanced disease only should be included with those with metastatic disease in trials evaluating systemic treatments. In phase II trials, this can heavily biaz the results, but stratification in the phase III trials can overcome the problem. Evaluation of