**143** INVITED

**The cell–matrix interaction in sarcoma**

I. Stamenkovic. *Switzerland*

Abstract not received.

**144** INVITED

**Chondrosarcoma subtyping: a hobby for the pathologist or important to find therapeutic targets?**

J.V.M.G. Bovee. *Leiden University Medical Centre, Pathology, Leiden, The Netherlands*

Conventional chondrosarcoma of bone constitutes approximately 90% of all chondrosarcomas. Conventional chondrosarcomas can be categorised according to their location in bone. The vast majority (>85%) is designated as primary central chondrosarcoma based on their location centrally within the medullar cavity. A minority (up to 15%) of conventional chondrosarcomas develop from the surface of bone as a result of malignant transformation within the cartilage cap of a pre-existent osteochondroma and is therefore called secondary peripheral chondrosarcoma. While central and peripheral chondrosarcoma are histologically similar, at the molecular genetic level they differ. EXT, the gene causing Multiple Osteochondromas, is involved in the origin of osteochondroma and peripheral chondrosarcoma. In central cartilaginous tumours EXT is not involved and the initiating event is still unknown. In addition, central and peripheral chondrosarcoma differ in their chromosome content and in the activity of signaling cascades. Therefore, when the biology of these two subtypes will be further unraveled, different targets for therapy may emerge enabling the design of future tailored therapy for central and peripheral chondrosarcoma.
In addition to conventional chondrosarcoma, several rare subtypes of chondrosarcoma are discerned, together constituting approximately 10% of all chondrosarcomas. Mesenchymal chondrosarcoma is a highly malignant lesion that can occur in bone and soft tissue of relatively young patients and is characterized by scattered areas of differentiated cartilage admixed with undifferentiated small round-cells. Dedifferentiated chondrosarcoma is a highly anaplastic sarcoma next to a (usually low-grade) malignant cartilage-forming tumour, with a remarkably sharp junction between both components, bearing an ominous prognosis. Clear cell chondrosarcoma is a tumour of low-grade malignancy characterized by tumour cells with clear, empty cytoplasm. Periosteal chondrosarcoma arises from the external surface of bone and is possibly of periosteal origin. The few molecular genetic studies on these rare chondrosarcoma subtypes reported so far suggest different molecular backgrounds for each subtype. Thus, chondrosarcoma subtyping is at present not only essential to estimate prognosis for optimal therapeutic decision making, it is also highly relevant to enable the identification of targets for the design of future adjuvant therapy since chondrosarcoma is notorious for its resistance to conventional chemo- and radiotherapy.

## *Special session* (Wed, 26 Sep, 13:30−14:30)
## Genetic predisposition to melanoma: from the gene to the patient and vice-versa

**145** INVITED

**Genetic predisposition to melanoma: high and low-risk genes and how to assess risk in the clinic**

J. Newton Bishop[1], N. Gruis[2], Melanoma Genetics Consortium[3]. [1]*Cancer Research UK, Genetic Epidemiology Division, Leeds, United Kingdom;* [2]*Leiden University Medical center, Skin Research Laboratory, Leiden, The Netherlands;* [3]*GenoMEL, www.genomel.org, International, United Kingdom*

**Background:** The melanoma genetics consortium GenoMEL is comprised of groups from around the world who are working to understand the genetics of susceptibility to melanoma, and how the susceptibility genes interact with the environment. www.genomel.org.
GenoMEL pool data from groups across Europe, Australia, North and South America. The aims are to:
1. Establish the gene penetrance for the most common high risk susceptibility gene, CDKN2A
2. Understand the risk of other cancers in gene carriers
3. Understand the relationship between susceptibility genes and particular patterns of sun exposure
4. Understand somatic events in primary tumours and to understand the impact ot germline CDKN2A mutations on the somatic mutations in primary tumours.
5. To find new high and intermediate susceptibility genes for melanoma
6. To develop risk alogorithms for melanoma based upon meta-analyses of large melanoma case-control studies
7. Understand the determinants of behaviour in the sun so that suitable advice for protection can be included in the risk algorithm.

**Results:** Germline CDKN2A mutations are associated with earlier age of onset of melanoma, the presence of multiple primaries and pancreatic cancer (at least in some countries). Inherited MC1R variants increased gene penetrance. The assessment of risk in the clinic is therefore dependent on these factors. The role of gene testing will be discussed. Use of an on-line sun exposure questionnaire in multiple countries to collect data on attitudes to the sun will be presented.

**146** INVITED

**Managing melanoma families in the clinic**

J. Hansson. *Karolinska University Hospital – Solna, Department of Oncology–Pathology, Stockholm, Sweden*

**Background:** Approximately 5−10% of melanoma cases occur in families with hereditary predisposition to melanoma. In a minority of such families the melanoma predisposition can be attributed to germline mutations in high risk genes such as CDKN2A or CDK4, but in the majority the predisposing genetic alterations are unknown. Programmes aimed at providing primary and secondary prevention to melanoma families have been established. The outcome of such activities is illustrated by a preventive program aimed at Swedish melanoma kindreds
**Materials and Methods:** In 1987 a program was initiated by the Swedish Melanoma Study Group with the aim to provide preventive surveillance to melanoma families. The program is carried out in 12 specialized outpatient clinics. All newly diagnosed melanoma cases are questioned regarding heredity and if additional melanoma cases are verified a pedigree is constructed and family members are invited through the proband to participate in the program. Participating family members are given information on sun protection and skin self-examination. Whole-skin examinations including photographic documentation and dermoscopy are performed with 6-monthly intervals. Nevi with changing appearance, as well as lesions that raise suspicion of melanoma development for other reasons, are excised for histopathologic examination. Genetic testing for germline CDKN2A mutations was performed as part of research protocols.
**Results:** Between 1987 and 2001 2,080 members of 280 melanoma families were followed. During follow-up 1,912 skin lesions were excised. Of these 53% were common nevi and 40% dysplastic nevi. In total 41 melanomas were removed in 32 individuals: 15 (37%) were in situ melanomas while 26 (63%) were invasive, with a median tumor thickness of 0.5 mm. Of the 32 patients diagnosed with melanoma during follow-up 21 (66%) had had at least one previous melanoma removed. All melanomas except one were diagnosed in families with two or more first degree relatives with melanoma. Diagnosis of melanoma occurred in 3 of 8 kindreds with germline CDKN2A mutations, supporting that this mutation is associated with a high risk for melanoma.
**Conclusions:** A coordinated program aimed at detecting and offering preventive activities in kindreds with hereditary cutaneous melanoma results in a low incidence of melanomas during the follow-up period and tumors that do arise have favourable prognostic characteristics.

**147** INVITED

**Phenotypic variation in familial melanoma: a handicap for offering DNA diagnosis to families**

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Familial melanoma (FAMMM syndrome) has been defined as the occurrence of two first degree relatives with invasive melanoma, or three or more melanoma patients on the same side of the family. Familial melanoma has similar characteristics as other familial cancer syndromes: tumors occur at younger ages, multiple primary tumors are frequent and a spectrum of other cancers types show increased incidences in the syndrome.
Today there are two major melanoma associated genes, one tumor suppressor gene and one oncogene with mutations already present in the germline, that cause hereditary melanoma: CDKN2A (chromosome 9p21) with gene products p16 and p14ARF and CDK4 gene (chromosome 12q14).
About 40% of all families with multiple melanoma cases (3 cases or more) exhibit a mutation in one of these genes, in the other families yet unknown mutations are supposed to be responsible for the trait.
Families with hereditary melanoma considerably vary with respect to many items, such as the presence of atypical nevi (AN), numbers of AN, the age at which melanomas start developing, the risk of and maximum number of multiple melanomas and the presence of other cancer types (specifically pancreatic carcinoma)