factor and cis-element, patient subgroups of different size can be selected in which transactivation via these promoter elements might be tumor-tissue-specific, suggesting subgroups for tumor-selective targeting. Also, the lecture will outline that different u-PAR-promoter motifs may be of different tumor-specificity in vivo. We will also suggest patient subgroups in which a synergistic regulation of u-PAR gene expression in resected tissues via both promoter elements can be postulated. Finally, potential conclusions for a more target-oriented patient selection and therapy out of transcriptional and oncogeneic regulators of the uPA-R gene will be discussed. The lecture will in part contain new, non-published data.

## *Keynote Lecture*
## Oncogenes and the future of cancer therapy

**57** INVITED

**Oncogenes and the future of cancer therapy**

H. Varmus. *Memorial Sloan Kettering Cancer Center, New York, USA*

Over the past thirty five years, several methods have been used to determine whether dominantly acting oncogenes that have been implicated in the initiation of tumorigenesis are also required to maintain the transformed state and the viability of cancer cells. These approaches include (i) the use of conditional [temperature-sensitive] mutants of retroviral oncogenes and, more recently, small inhibitory RNA's that target oncogenic mRNA's in an allele-specific fashion; (ii) the generation of transgenic mice in which oncogenes or their protein products can be activated and then deactivated (e.g. by the use of antibiotic-dependent systems for gene induction or hormone-sensitive fusion proteins); and (iii) the introduction of protein-specific inhibitory agents, mainly small molecules and antibodies, that can be examined for therapeutic effects in patients, as well as in experimental animals and cell culture.

A striking and encouraging theme has emerged from these various strategies: the idea that, in general, cancer cells seem to be dependent on one or a few activated oncogenes for maintenance of their oncogenic status and even for cell viability. This implies that, for any cancer, it might be possible to control and even eliminate tumor cells with one agent or a small combination of targeted drugs or antibodies, despite extensive genetic changes in the cancer cell. To accomplish this, it will be necessary to catalog in more detail the genotypes of the many kinds of human cancer and to discover more therapies targeted specifically against more of the many genes and proteins that have been implicated in carcinogenesis by gain-of-function mutations.

I will discuss recent studies of lung adenocarcinomas arising spontaneously in human patients or induced in mice with oncogenes belonging to the Ras and epidermal growth factor receptor families. Information about oncogene-dependence of tumors in the mouse models, about the importance of genotypes in the selection of drugs to treat human lung cancer, and about the role of secondary mutations in acquired resistance to inhibitors of protein-tyrosine kinases will be used to advance the case that most or all cancers will ultimately become highly controllable disorders.

## *Young Oncologists session*
## Life after cancer treatment

**58** INVITED

**Persistent fatigue in cancer survivors: biological basis and clinical management**

P.A. Ganz. *UCLA Jonsson Comprehensive Cancer Center, Division of Cancer Prevention & Control Research, Los Angeles, USA*

Fatigue is one of the most commonly reported symptoms for patients receiving cancer treatment and this may persist beyond the acute phase of treatment among cancer survivors. Persistent fatigue is reported by as many as 30% of breast cancer survivors, and is also a frequent complaint for other survivors (e.g. Hodgkin's disease). Persistent fatigue is often associated with pain and depressive symptoms; however, it is uncertain if these associations represent cause or effect. In our laboratory, we have been studying some of the biological and psychological mechanisms of fatigue in cancer survivors, and these will be explored in this presentation. Strategies to address fatigue in the clinic are multifactorial and depend on the etiology of the symptom.

**59** INVITED

**Management of long-term sequellae in patients with Hodgkin's disease**

A. Sureda. *Hospital de la Santa Creu i Sant Pau, Department of Hematology, Barcelona, Spain*

The survival of patients treated for Hodgkin's lymphoma (HL) has improved dramatically as a result of the development of multiagent chemotherapy, more accurate radiotherapy (RT), and enhanced possibilities to treat complications during and after treatment. Nevertheless, it is evident that the average survival for HL patients does not return to normal after treatment when compared with age-matched general population. The two major causes of mortality excluding HL in the long-term survivors are secondary malignancies and cardiovascular disease (CVD). When compared with the general population, the leukaemia risk in HL patients is 10 to 80 higher. The risk period for leukaemia is predominantly within the first 10 years. Young females who receive thoracic RT are at high risk of developing breast cancer. There was no increased risk for patients >30 years but the risk was 56 times greater for patients $\leqslant$19 years old. HL patients have also an increased risk of developing lung cancer, sarcomas, melanomas and thyroid cancer. With respect to CVD, the relative risk of death from cardiac disease has been estimated to increase 3.1 times with the highest risk group being that of young patients treated with mediastinal RT. Other long-term complications include infectious episodes, pulmonary fibrosis, osteonecrosis, hypothyroidism and gonadal dysfunction. Finally, fatigue levels of patients with HL are high, even years after treatment. From a management point of view, it is important to pay attention to possible signs of malignancies – especially of the digestive and respiratory tract and especially in patients treated at young ages. For women who have been irradiated before age 30, screening is urged because of the highly elevated risk of developing breast cancer. Pneumococcal vaccination and instructions on the use of antibiotics are recommended after splenectomy. Patients treated for HL should be advised to refrain from smoking, because smoking acts synergistically with RT in the development of lung cancer and, potentially, CVD. Timely intervention in other risk factors of CVD may help to reduce its high absolute excess risk in survivors of HL. Finally, the development of risk-adapted therapeutical strategies based on new developments in diagnostic testing and enhanced understanding of the basic pathogeneic mechanisms of HL, including molecular profiling, may also assist in the identification of specific prognostic groups that might receive different therapies.

**60** Abstract not received