## Tuesday 7 November 13:15–14:00

# Michel Clavel lecture

**1** INVITED

**Targeted therapies**

J. Baselga. *Spain*

Abstract not received.

## Tuesday 7 November 14:00–14:45

**KEYNOTE LECTURE**

# Keynote Lecture

**2** INVITED

**Implications of breast cancer stem cells**

F. Clarke, H. Karel, A.N. Beekhuis. *Stanford Institute for Stem Cell Biology and regenerative medicine, Palo Alto, USA*

Most common cancers arise in organs such as the breast that contain a small population of stem cells that constantly replenish the mature cells of the tissue. Stem cells are defined by the ability to divide and give rise to a new stem cell (self-renewal), as well as the ability to give rise to the differentiated cells of an organ, and thus are the only long-lived cells in many tissues. Solid tumors consist of a heterogeneous population of cancer cells which differ in their apparent state of differentiation, suggesting that solid tumors might represent aberrant organs containing a cancer stem cell population that maintains the ability to self-renew. Indeed, using a xenograft model of human breast cancer, a small, phenotypically-distinct subset of the cancer cells (cancer stem cells) has been found to have the exclusive ability to form tumors. The remaining cancer cells, which form the bulk of the tumor, are unable to self-renew or sustain tumorigenesis. Recently, it has become apparent that some oncogenes and tumor suppressor genes also regulate self-renewal, the process by which both normal and malignant stem cells maintain themselves. The process of self-renewal is de-regulated in cancer stem cells resulting in tumor formation. It is likely that targeting cancer cell self-renewal pathways will result in more effective cancer therapies.

## Tuesday 7 November 15:15–17:00

**PLENARY SESSION 1**

# Apoptosis and other cell death mechanisms

**3** INVITED

**Targeting apoptosis in cancer with Apo2L/TRAIL**

A. Ashkenazi. *Genentech, Department of Molecular Oncology, South San Francisco, CA, USA*

Recombinant human Apo2L/TRAIL activates the pro-apoptotic receptors DR4 and DR5. Upon binding to DR4 and/or DR5, Apo2L/TRAIL assembles a molecular signaling complex that activates the apoptosis-initiating proteases caspase-8 and 10. These initiator caspases in turn stimulate effector caspases, such as caspase-3, 6 and 7, which carry out the apoptotic cell death program. Unlike most conventional cancer therapeutic agents, Apo2L/TRAIL activates the apoptotic caspase cascade independently of the p53 tumor suppressor gene. As a soluble, zinc-coordinated trimer, Apo2L/TRAIL selectively induces apoptosis in various types of tumor cells while sparing normal cells. In mouse xenograft models of solid tumors, including colorectal and non-small cell lung cancer, Apo2L/TRAIL displays single agent anti-tumor efficacy as well as cooperation with chemotherapy. Furthermore, in models of non-Hodgkin's lymphoma, Apo2L/TRAIL demonstrates single agent activity and cooperates with anti-CD20 antibody therapy. Preclinical safety studies in non-human primates have demonstrated that systemic infusion of Apo2L/TRAIL is well tolerated. Phase I clinical trials assessing the safety and pharmacokinetics of Apo2L/TRAIL in cancer patients are in progress.

**4** INVITED

**Clinically used agents to induce apoptosis especially targeting the TRAIL-receptors**

E.G.E. de Vries, S. de Jong, C.H. Mom, J.A. Gietema. *University Medical Center Groningen, Department of Medical Oncology, Groningen, The Netherlands*

Apoptosis induction can result in tumor shrinkage. It can be executed through a mitochondria-dependent (instrinsic) and a mitochondria independent (extrinsic) pathway. The "extrinsic" pathway is initiated by activation of cell membrane death receptors. The TRAIL pathway is currently explored in the clinic. The natural occurring death receptor ligand TRAIL, can induce apoptosis in tumor cells and not in normal cells by binding to its cell membrane death receptors (DR) 4 and DR5. Soluble, zinc-stabilized recombinant human (rh)TRAIL without His-tag showed no preclinical toxicity. In a phase 1 study with rh Apo2L/TRAIL, which activates both DR4 and DR5, patients received once daily for 5 days every 3 weeks doses of up to 15 mg/kg. No drug-related, dose limiting toxicities were seen. Pharmacokinetic analysis showed a half-life of 36 min. One partial response occurred in a patient with chondrosarcoma at 8 mg/kg. Currently also agonistic DR4 and DR5 antibodies against DR4 or DR5 are studied in the clinic as another option to induce apoptosis. The phase 1 studies with agonistic DR4 antibody mapatumumab showed that it is well tolerated at doses up to 20 mg/kg per cycle. Mean terminal half-life was 17 days. Phase 2 studies with single agent mapatumumab administered in pretreated NSCLC and colorectal cancer patients showed stable disease in resp. 29% and 32%. In a non-Hodgkin's lymphoma study in 3 out 40 patients tumor responses have been observed, all in refractory or relapsed follicular lymphoma patients. In the preclinical setting a synergistic effect was observed between death receptor ligands and chemotherapy. There are 2 phase 1b studies in which mapatumumab is combined with gemcitabine/cisplatin (ongoing) and paclitaxel/carboplatin. The maximum tolerated dose is not yet reached. No pharmacokinetic interaction between the drugs was seen. Data on DR5 antibodies are only available for one antibody, lexatumumab. Two phase 1 studies have been performed. A dose of 10 mg/kg per cycle was considered the maximum tolerated dose. Based on preclinical data, combinations with numerous targeted agents are also of interest. Hopefully choices for specific (modified) death receptor ligand treatment can in the future be rationally made based on tumor characteristics.

**5** INVITED

**Involvement of Bcl-2 family proteins in Gleevec's mechanism of action**

A. Strasser[1], A. Villunger[2], P. Bouillet[1], E. Michalak[1], L. O'Reilly[1], D. Huang[1], P. Kelly[1], L. Coultas[1], E. Naik[1], M. Erlacher[2]. [1]*The Walter and Eliza Hall Institute of Medical Research, Molecular Genetics of Cancer Division, Parkville, Australia;* [2]*University of Innsbruck, Institute for Pathophysiology, Innsbruck, Austria*

Genetic and biochemical experiments have demonstrated that BH3-only proteins are essential for initiation of programmed cell death and stress-induced apoptosis and that Bax/Bak-like proteins are required for this process, probably functioning downstream. Different BH3-only proteins are required for cell death induced by different stimuli and they can also function in a cell type-specific manner. Bim is required for the death of many cell types triggered by growth factor withdrawal, for deletion of autoreactive lymphocytes and for termination of cytotoxic T cell (CTL) immune responses. The apoptosis provoked by DNA damage requires the p53 tumor suppressor and this death is dependent on the BH3-only protein Puma and to a lesser extent also Noxa. Surprisingly, Puma was found to also be essential for apoptosis induced by several p53-independent stimuli, including cytokine withdrawal or treatment with glucocorticoids or phorbol ester. Experiments with non-transformed cells and tumour cells have demonstrated that BH3-only proteins are essential for anti-cancer therapy-induced cell killing. Puma is required for apoptosis induced by ?-radiation or several widely used chemotherapeutic drugs, including etoposide or dexamethasone. Bim, on the other hand is needed for the death of chronic myelogenous leukemia (CML) cells triggered by the BCR-ABL kinase inhibitor Gleevec.