Cancer stem cells were significantly reduced after treating with uroacitide as monolayer cultures (MCF-7: the research is ongoing; MDA-MB-231: monolayer cultures, non-uroacitide = 37.31%, versus 1mg-uroacitide = 4.11%, 2mg-uroacitide = 4.89%, 3mg-uroacitide = 5.87%, P<0.01).

Conclusions: CD44+/CD24−/low cancer stem cells exist in MCF-7 and MDA-MB-231 cell lines. Wnt and Notch signal pathways are active in breast cancer stem cells, which are isolated in both cell lines. CD44+/CD24−/low cancer stem cells can be differentiated by uroacitide in MDA-MB-231 cell line. We postulate that targeting breast cancer stem cells will be becoming most interesting molecule level for those refractory and metastasized breast cancer patients.

The application of monoclonal antibody in mCRC

Jin Li
Fudan University Cancer Hospital, Department of Medical Oncology, Dong An Road, 200032 Shanghai, China

Colorectal cancer (CRC) is the fourth most common form of cancer worldwide and a major cause of morbidity and mortality in deaths in the United States and Europe. The 5-year survival rate for stage I disease is about 85–90%, but this falls to around 5% once patients develop stage IV disease. The last decade has ushered in exciting new advances for treating the patients with colorectal cancer. Targeted therapies, including monoclonal antibodies against vascular endothelial growth factor (bevacizumab) and the epidermal growth factor receptor (cetuximab), are now standard treatment for metastatic colorectal carcinoma. Based on successful randomized phase III trials, anti-EGFR and anti-VEGF therapeutics have entered clinical practice. Cetuximab (Erbitux), an EGFR-specific antibody, is currently approved in the United States in combination with irinotecan (Camptosar) for patients with metastatic colorectal cancer refractory to irinotecan or as a single agent for patients unable to tolerate irinotecan-based therapy. Bevacizumab (Avastin), a VEGF-specific antibody, was the first antiangiogenic agent to be approved in the United States for use in combination with standard chemotherapy in the first- and second-line of treatment in metastatic colorectal cancer. The application of monoclonal antibodies will promise higher response rate a longer survival time for colorectal cancer patients.

New cyclin-dependant kinase inhibitors as potential anti-tumor agents

Hervé Galons, Laurent Meijer, Nassima Oumata, Karima Bettayeb
INSERM 648 université René Descartes - Paris V, avenue de l’Observatoire, Paris75006, France

Among the eight pharmacological inhibitors of cyclin-dependent kinases (CDKs) currently in clinical trials, the purine roscovitine (CYC202, Seliciclib) is undergoing phase 2 trials against NSC lung and nasopharyngeal cancers. An extensive medicinal chemistry study, designed to generate more potent analogues of roscovitine has been undertaken. Several series of 2,6,9-trisubstituted purines, structurally related to roscovitine, have been prepared. They mainly differ by the substituent on the C-6 position: 6-aryl, 6-aminobaryl, 6-aminomethylene-aryl and 6-aminomethylene-biaryl. These compounds were screened for kinase inhibitory activities and antiproliferative effects. Several biaryl derivatives displayed potent inhibition of both CDKs and CK1 led to the identification of an optimal substitution at the N6 position (compound CR8). An extensive selectivity study (108 kinases) highlights the exquisite selectivity of CR8 for CDK1/CDK2/CDK3/CDK5/CDK7/CDK9. CR8 was 2-4 fold more potent than (R)-roscovitine at inhibiting these kinases. Co-crystal structures of (R)-CR8 and (R)-roscovitine with pCDK2/cyclin A showed that both inhibitors adopt essentially identical positions. The cellular effects of CR8 and (R)-roscovitine were investigated in human neuroblastoma SH-SY5Y cells. CR8 inhibited the phosphorylation of CDK1 and CDK9 substrates, with a 25-50 times higher potency compared to (R)-roscovitine. CR8 was consistently more potent than (R)-roscovitine at inducing apoptotic cell death parameters: MTS reduction (40 fold), LDH release (35 fold), caspases activation (68 fold), PARP cleavage (50 fold). This improved cell death inducing activity of CR8 over (R)-roscovitine was observed in 25 different cell lines. Altogether these results show that second generation analogs of (R)-roscovitine can be designed with improved anti-tumor potential.