Institute of Molecular and Cell Biology
A*STAR

SEMINAR ANNOUNCEMENT

We would like to invite you to attend this seminar hosted by Dr. Zeng Qi:

Date: 26 November 2014, Wednesday
Time: 11:00AM – 12:00PM
Venue: Level 3, IMCB Seminar Room 3-46, Proteos, Biopolis

Speaker: Prof. Soldano Ferrone, Faculty Member, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA
Title: Chondroitin sulphate proteoglycan 4 (CSPG4), an attractive target of antibody-based immunotherapy in various types of solid tumors.

Like CD44 (CSPG8), the tumor cell membrane-bound CSPG4, also known as high molecular weight-melanoma associated antigen (HMW-MAA), or neuron-glial antigen 2 (NG2), is a member of the CSPG family. CSPGs are key bioactive molecules that play a major role in tumor growth, migration and neo angiogenesis. CSPG4 is a unique glycoprotein-proteoglycan complex consisting of a 250 kDa N-linked glycoprotein and a 450 kDa proteoglycan component. It is composed of three major structural components: the extracellular domain (consisting of 3 subdomains), the transmembrane region, and the cytoplasmic C-terminal domain (CTD). This tumor antigen associates with platelet-derived growth factor receptor (PDGFR)-α, integrins a3b1 and a4b1. STAT5A may be involved in regulating CSPG4 expression since there're potential binding sites of STAT5A located in CSPG4 promoter region.

Flow cytometry analysis of established cancer cell lines stained with mAbs and immunohistochemical staining of surgically excised tumors from patients have shown that CSPG4 is expressed on glioma, squamous cell carcinoma of the head and neck (SCCHN), esophageal squamous cell carcinoma, triple negative breast cancer (TNBC), melanoma, mesothelioma, renal cell carcinoma, chordoma, chondrosarcoma, osteosarcoma, soft tissue sarcomas, and acute leukemia. On most malignant cells CSPG4 has a high expression with limited intra- and inter-lesional heterogeneity. It is noteworthy that CSPG4 is expressed not only on differentiated malignant cells, but also on cancer initiating cells (CICs). Therefore targeting CSPG4 may eliminate not only differentiated cancer cells, but also CICs. In contrast CSPG4 has a restricted distribution in normal tissues. It is expressed on activated pericytes in the tumor microenvironment. CSPG4 upregulation on activated pericytes may be due to the hypoxic conditions in the tumor microenvironment, since we have found that CSPG4 expression is upregulated on TNBC cells incubated under hypoxic conditions. As a result immunotargeting of CSPG4 inhibits neo angiogenesis and growth of tumor cells, even those which do not express CSPG4.

The structural and functional properties of CSPG4 are highly conserved through phylogenetic evolution. The high degree of homology, but not complete identity among CSPG4s in various animal species accounts for their ability to overcome unresponsiveness to self-CSPG4 in xenogeneic hosts. This mechanism accounts for the ability of DNA encoding human CSPG4 in combination with electroporation to elicit humoral immunity to self-CSPG4 in dogs with melanoma. In agreement with results obtained in patients with melanoma immunized with CSPG4 mimics, this immunity appears to have clinical significance, since it is associated with a favorable clinical course of the disease.

Most, if not all the available CSPG4-specific mAb are not effective in mediating complement- and cell-dependent lysis of tumor cells. On the other hand, the few CSPG4-specific mAb used have been very useful to generate chimeric antigen receptors (CARs) to redirect T cells to tumors expressing this tumor antigen. T cells transduced with CSPG4-specific CARs have been shown to lyse CSPG4 expressing human tumor cells *in vitro* and to inhibit the growth of CSPG4 expressing human tumor cells grafted in immunodeficient mice. Furthermore CSPG4-specific mAbs are very effective in inhibiting both *in vitro* and *in* vivo signal transduction pathways associated with tumor cell proliferation, survival and migration. These results provide a mechanism(s) for the ability of CSPG4-specific mAbs to inhibit tumor growth, and more importantly disease recurrence and metastatic spread in immunodeficient mice grafted with human melanoma, TNBC or mesothelioma cells. Lastly, we have found that the anti-tumor effect of CSPG4-specific mAb is enhanced by the sonic hedgehog homolog (SHH) pathway inhibitor LDE225. In particular, CSPG4-specific monoclonal antibodies in combination with LDE225 have been found to be able to eradicate cancer initiating cells.

Biography:
Soldano Ferrone received his MD and PhD degrees in 1964 and in 1971, respectively, from the University of Milan, Milan, Italy. He has held faculty positions at the University of Milan, Milan, Italy, Scripps Clinic and Research Foundation, La Jolla, CA, Columbia University, New York, NY, New York Medical College, Valhalla, NY, Roswell Park Cancer Institute, Buffalo, NY and at the University of Pittsburgh School of Medicine, Pittsburgh, PA. Since 2012 he is a faculty member of the Department of Surgery at Massachusetts General Hospital, Harvard Medical School, Boston, MA. Dr. Ferrone has received many awards and honors. For the last 30 years he has been the member of many review committees including NIH Study Sections, and of the editorial boards of many scientific journals. Furthermore he is the member of several external scientific boards. Dr. Ferrone's research program focuses on the molecular characterization of escape mechanism(s) utilized by tumor cells to avoid immune recognition and destruction and on the development of combinatorial immunotherapeutic strategies to counteract the escape mechanism(s) utilized by tumor cells. These studies are greatly facilitated by the large panel of HLA antigen- and human tumor antigen-specific monoclonal antibodies he has developed and shared with the scientific community over the years. He has described the results of his studies in more than 600 papers published in peer reviewed journals. Moreover he has been the editor of 14 books and the guest editor of 5 special issues of oncology journals.

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