#2175 Synthetic antigen receptor mesenchymal stem cells (SAR-MSCs) targeting perlecan for drug delivery to ovarian cancer. Susheel Kumar Nethi, Dristhi Sehgal, Shen Cheng, Jayanth Panyam, Swayam Prabha. *University of Minnesota, Minneapolis, MN.*

Mesenchymal stem cells (MSCs) can be engineered with polymeric nanoparticles for tumor-targeted delivery of small molecule drugs. Such nano-engineered MSCs have demonstrated exciting anticancer activity in multiple ovarian cancer models. Despite significantly improved delivery of chemotherapeutics to tumor tissues, non-specific accumulation of MSCs in clearance organs remains a concern. Paralleling the concept of CAR-T cells, we advance here a strategy for synthetic modification of MSCs with antibodies targeting specific antigens over-expressed on cancer cells. Our approach consists of stably incorporating recombinant protein G (PG) on the surface of MSCs, followed by binding of a full-length IgG to the PG handle. Because protein G binds to the Fc region of IgG, antigen-binding affinity of the antibody is conserved. We have previously shown the overexpression of perlecan (HSPG2) on ovarian cancer cells and its correlation to poor patient survival. In the current study, we investigated the incorporation of anti-perlecan antibody on the surface of nano-engineered MSCs. The anti-perlecan IgG antibody was first derivatized with palmitic acid (PA), which was then used to insert PG on MSCs cell membrane. We characterized the PAPG derivative by LC/Q-TOF/MS. Flow cytometry and confocal microscopy were used to confirm the incorporation of fluorescently labeled PAPG handle on MSC surface. Similarly, the binding of fluorescently labeled anti-perlecan IgG to PAPG-functionalized MSCs was confirmed by flow cytometry. We are currently investigating the anticancer efficacy of paclitaxel-loaded, anti-perlecan SAR-MSCs using in vitro and mouse models of ovarian cancer.

#2176 Topical delivery of carvedilol-loaded transfersomes for photoprotection and skin cancer prevention. Mengbing Chen, Mengbing Chen. *Western University of Health Sciences, Pomona, CA.*

Ultraviolet (UV)-induced skin cancer is the most common cancer diagnosed in the United States and remains one of major public health concerns. Thus, there is an urgent need for the development of more effective strategies to prevent and treat skin cancer. We have previously demonstrated that carvedilol, an FDA approved β-blocker for cardiovascular diseases, could prevent UV-induced skin cancer both in vitro and in vivo. However, the β-adrenergic blockade effects of carvedilol might be a barrier for its repurposing as a cancer chemopreventive agent due to its cardiovascular side effects. In this work, we aimed to design a novel topical formulation, namely carvedilol-loaded transfersomes, which could maintain anti-cancer activities but avoid systemic cardiovascular effects. Carvedilol-loaded transfersomes were prepared using different phospholipids and surfactants at various ratios by a thin-film hydration method. Following optimization of preparation, the transfersomes were characterized in terms of particle size, zeta potential, and encapsulation efficiency. Skin permeation studies were performed using Franz vertical diffusion cells and skin dissected from SKH-1 hairless mice to examine the permeability of carvedilol. An optimal formulation was identified to compose carvedilol, Soy PC, and Tween-80 at a ratio of 1:3:0.5. The particle size, zeta potential and encapsulation efficiency for this formulation were determined to be 162.9$\pm$9.6 nm, 17.1$\pm$0.3 mV and 47.9$\pm$3.5%, respectively. Skin permeation studies showed that the specific carvedilol-loaded transfersomes could not penetrate through the skin layers in comparison with free carvedilol dissolved in acetone. Taken together, these results suggest that the transfersomal formulations of carvedilol may have desirable physical and biological characteristics for skin retention and local action. Ongoing studies are focused on further improvement of encapsulation efficiency and determination of its effectiveness against skin cancer.

#2177 Streptavidin-pHast: A readily conjugatable, pH-sensitive dye to screen for internalization. Patrick A. Shramm, Leonardo Ancheta. *CytoLogistics, San Diego, CA.*

Quick and efficient screening of targeting agents that internalize effectively is vital for determining their suitability as potential therapeutics. Some of the most recent successes in the treatment of cancers have been from antibodies to cell surface proteins that are responsible for tumor cell proliferation. Examples are Cetuximab (target: EGFR) approved for colorectal cancer, and Trastuzumab (target: HER2) for breast cancer. These antibodies have more than one effect on the cancer cell, but one of the most important is that, upon binding to the cell surface antigen, the complex is internalized. As such, the down-regulated cell surface protein no longer plays a role in cancer cell division. Here we describe a method for determining internalization of cell surface molecules by targeting agents using a pH-dependent fluorescent reporter cross-linked to streptavidin. Streptavidin is a tetrameric protein (molecular weight 53 kDa in its recombinant form), with each subunit able to bind a single biotin molecule. The bond between streptavidin and biotin is rapid and essentially non-reversible, unaffected by most extremes of pH, organic solvents, and denaturing reagents. It is the strongest known noncovalent biological interaction (Ka = 10^{15} M^{-1}) between protein and ligand. A variety of molecules, including lectins, proteins, and antibodies, can be biotinylated and reacted with streptavidin-labeled probes or other detection reagents for use in biological assays. The fluorescence from this reporter increases intensity as the pH of its surroundings becomes more acidic, as demonstrated when exposed to the environment inside a cell (thereby providing evidence of internalization). Here we describe methods that can be used to explore candidates as cancer therapeutics in a quick, reliable and reproducible manner.

#2178 Targeted delivery of chemotherapeutic agents employing nanovesicles effectively reduced intrahepatic tumors. Joseph George, Nobuhiko Hayashi, Takashi Saito, Mikihiro Tsutsumi, Mutsumi Tsuchishima. *Kanazawa Medical University, Hepatology, Uchinada, Ishikawa 920-0293, Japan.*

Background and Aims: Currently there is no appropriate method for effective and targeted delivery of chemotherapeutic agents to tumor sites. The conventional chemotherapy is afflicted with lack of effective drug delivery to the tumor site, unwanted injury to actively dividing healthy cells, and numerous side effects due to toxicity. The present study was aimed to develop a biologically derived nanoparticle based drug delivery system for the effective treatment of primary hepatic tumors. Methods: Intrahepatic tumors were induced in immunosuppressed mice using PLC/PRF/5 hepatocellular carcinoma (HCC) cells stably transfected with a mammalian expression vector carrying luciferase gene for in-vivo imaging. Nanovesicles ranging from 80-150 nm were isolated from bovine skim milk using ultracentrifugation and characterized using nanoparticle tracking analysis (NTA) and electron microscopy. Purified nanovesicles were loaded with chemotherapeutic agents and antisense oligonucleotides for grossly deregulated microRNAs specific to HCC. Animals with uniform intrahepatic tumors were injected with nanovesicle loaded anticancer agents through tail vein. Tumor regression was monitored weekly using in-vivo imaging system and the animals were maintained up to 8 weeks. Results: Bioluminescence based in-vivo imaging demonstrated significant reduction of tumor size in treated animals compared to untreated controls. There was increased survival rate and complete absence of metastasis in all treated animals. Untreated mice developed large intrahepatic tumors, which also metastasized to other organs. There were no side effects or immunological reactions in animals injected with plain nanovesicles without loading of any anticancer agents. Conclusions: The present study demonstrated that milk derived nanovesicles can be effectively used for successful delivery of anticancer agents into intrahepatic tumors. Nanovesicle based targeted drug delivery system could be an effecient method for the treatment of primary hepatic tumors.* Presenting author E-mail: georgej@kanazawa-med.ac.jp.

Novel Therapeutics and Pathways

#2179 Antitumor activity of JNJ-63576253 (TRC253), a small molecule antagonist of F877L mutant and wild-type androgen receptor. Tammy L. Bush,[1] Georges Habineza Ndikuyeze,[1] Gilles Bignan,[1] Jonathan Branch,[1] Janine Ondrus,[1] Yifan Shi,[1] Leopoldo Luistro,[1] James Hastings,[1] Joseph Erhardt,[1] Ian Hickson,[2] Shefali Patel,[1] Peter Connolly,[1] Zhuming Zhang,[1] James Bischoff,[3] Brent Rupnow,[1] Marco Gottardis,[1] Kathryn Packman[1]. *[1]Janssen Research and Development, Spring House, PA; [2]Newcastle University, Newcastle upon Tyne, United Kingdom; [3]Roche, Grenzacherstrasse, Basel, Switzerland.*

Androgen receptor (AR) antagonists have transformed prostate cancer patient care by targeting a key nodal point in tumor cell signaling. However, despite the impressive clinical activity of first- and second-generation antiandrogens, acquired resistance frequently emerges. Point mutations in the ligand-binding domain of AR, such as phenylalanine to leucine at position 877 (AR^{F877L}), account for 10-20% of resistance. Such mutations are characterized by receptor activation, rather than inhibition, by first- and second-generation antiandrogen therapeutics. JNJ-63576253 is a potent, high affinity competitive binder of wild type and mutant AR, including F877L. JNJ-63576253 blocks AR nuclear translocation, AR binding to DNA, and AR-dependent transcription. JNJ-63576253 inhibits the proliferation of androgen receptor driven prostate cancer cell lines, including those bearing AR^{F877L}. In the Hershberger assay in male Sprague Dawley rats, oral administration of JNJ-63576253 inhibited androgen sensitive organ (ASO) development in a dose-dependent manner. In male SHO mice bearing LNCaP xenografts with either wild-type or AR^{F877L},