Stephenson School of Biomedical Engineering
Seminar Series Presents

DEVELOPMENT OF A CANCER DRUG THAT DISRUPTS ONCOGENIC HEAT SHOCK PROTEIN A/CLIENT PROTEIN INTERACTIONS

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zoom

Meeting ID: 759 581 394
Call in: 602 753 0140

ABSTRACT

Sulfur heteroarotinoid A2 (SHetA2) is a small molecule drug that was identified in a screen for compounds that kill cancer cells without harming healthy cells. Drug conjugated magnetic microparticles were used to identify three homologous heat shock protein As (HSPA9/mortalin, HSPA8/hsc70 and HSPA5/Grp78) as SHetA2 binding proteins. These proteins function as molecular chaperones that assure proper folding and localization of client proteins and protein complexes. NMR and SPR analysis demonstrated that SHetA2 binds to the peptide binding domain of mortalin with a 10 μM binding constant. Co-immunoprecipitation assays of treated and control cancer cells demonstrated that SHetA2 causes release of client proteins from mortalin. Western blot and cell imaging studies documented that SHetA2 disruptions of HSPA complexes result in the client proteins either being degraded or relocated within the cell. Comparison of healthy and cancer cells revealed that HSPAs are elevated in cancer cells to protect them from deleterious effects of over-expressed oncogenic client proteins, such as p53, or to provide stability to overexpressed complexes that drive cell proliferation, such as the cyclin D1/cyclin dependent kinase 4/6 (CDK4/6) complexes. Combination of SHetA2 with drugs targeted at p53 or CDK4/6 demonstrated synergistic interaction in cell culture and at least additive interaction in animal models with anti-angiogenic activity and no toxicities detected. National Cancer Institute (NCI) RAID, RAPID and PREVENT Programs provided the preclinical testing and drug capsule production needed to submit an Investigational New Drug (IND) application to initiate first-in-human SHetA2 clinical trials. This testing found that SHetA2 was not toxic, mutagenic, carcinogenic, teratogenic or irritating to skin at doses 50 fold above the doses that prevent and reduce tumor burden in animal models. NCI R01 grants are funding a Phase 1 clinical trial of SHetA2 in advanced or recurrent gynecologic cancers at the Stephenson Cancer Center anticipated to provide a recommended phase 2 dose (RPh2D) by the summer of 2021. Plans are in development to use the RPh2D of SHetA2 in combination with paclitaxel chemotherapy, a p53 inhibitor or CDK4/6 inhibitor in future Phase 1b/2 clinical trials. Suppository, intrauterine delivery and inhaled formulations are in development for application of SHetA2 as a chemoprevention agent.

BIO

Dr. Benbrook obtained her Ph.D. degree in biochemistry at Loyola University Medical School in Illinois, and received post-doctoral training from Burnham Institute in California. She has published over 100 peer-reviewed journal articles and book chapters. She holds multiple US patents for her inventions. Dr. Benbrook has been the co-leader of the Gynecologic Cancers Program in Stephenson Cancer Center since 2016 and the director of Research in Gynecologic Oncology since 1993. She has also served as the director for Women's Cancer Program and co-chair of the scientific advisory committee for the Stephenson Cancer Center. She has been awarded the Presbyterian Presidential Professorship since 2019 and master mentor for the Oklahoma Shared Clinical and Translational Resources since 2018. She has been named the Woman of the Year - 50 Making a Difference twice, Innovator of the Year twice, Oklahoma Scientist of the Year in 2004, and won the First Place for best business plan in Oklahoma Governors Cup Competition (Received) in 2009.

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