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An estrogen receptor α (ERα)-BMPR2-apelin axis mediates 17β-estradiol's protective effects on right ventricular function in experimental pulmonary hypertension (PH)

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OBJECTIVES/SPECIFIC AIMS: Women with pulmonary arterial hypertension (PAH) exhibit superior right ventricular (RV) function and survival compared with men, a phenomenon attributed to poorly understood cardioprotective effects of 17β-estradiol (E2). We hypothesize that E2, through ERα, attenuates PH-induced RV dysfunction by upregulating the pro-contractile and pro-angiogenic peptide apelin. This ERα-mediated increase in apelin is mediated by the myocardial remodeling effector bone morphogenetic protein receptor 2 (BMPR2). METHODS/STUDY POPULATION: ERα, BMPR2, and apelin were measured (western blot) in RVs from patients with PAH-induced RV failure and in RV homogenates from male or female Sprague-Dawley rats with sugen/hypoxia (SuHx) or monocrotaline (MCT)-induced PH. H9c2 rat cardiomyoblasts and cardiac endothelial cells were stressed with TNF-α (10 ng/mL) or staurosporine (50 nM) ± E2 (100 nM; 24 h). ERα-, BMPR2-, and apelin-dependence were evaluated by siRNA (5 pM). Downstream apelin target and pro-survival factor ERK1/2 expression was measured (western blot). $p < 0.05$ by ANOVA was considered significant. RESULTS/ANTICIPATED RESULTS: ERα correlated positively with BMPR2 and apelin expression in SuHx-RVs and human RVs. Treatment of SuHx-PH rats with E2 or ERα agonist increased RV BMPR2 and apelin, whereas RV apelin was decreased in E2-treated hypoxic ERα knockout mice ($p < 0.05$), but not in ERβ knockout mice. In H9c2 cells, E2 or ERα agonist attenuated TNF-α- or staurosporine-induced decreases in BMPR2, apelin, and phospho-ERK1/2 ($p < 0.05$ for all endpoints). E2 protection was lost in presence of siRNA directed against ERα, BMPR2, or apelin ($p < 0.05$). ERα was necessary for E2-mediated increases in BMPR2, apelin, and ERK1/2, and BMPR2 was required for the E2-mediated increase in apelin ($p < 0.05$ for siRNA vs. scramble). ERα, BMPR2, and apelin protein was increased in decompensated human RVs but downstream phospho-ERK signaling was disrupted. DISCUSSION/SIGNIFICANCE OF IMPACT: E2, via ERα, increases BMPR2 and apelin in the failing RV and in stressed rat cardiomyoblasts. The E2-mediated increase in apelin is BMPR2-dependent and likely occurs through direct binding of ERα to the BMPR2 promoter. Harnessing this E2-ERα-BMPR2-apelin axis during RV compensation may lead to novel, RV-targeted therapies for PAH patients of either sex.

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Vaccine efficacy and immunogenicity of recombinant WAP and CAP-1 proteins in AKR mice

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OBJECTIVES/SPECIFIC AIMS: *Trichuris trichiura*, is a leading cause of chronic colitis worldwide, resulting in growth stunting, anemia, and cognitive deficits, predominately in children. Our long-term goal is to develop a vaccine against *T. trichiura*. Both *T. trichiura* and the closely related *Trichuris muris* release excretory/secretory (ES) macromolecules from the stichosome organ, which facilitates intracellular invasion into the cecum. We exploited the high degree of genetic sequence homology between *T. trichiura* and *T. muris* to evaluate *T. muris* stichosome proteins as vaccine candidates. METHODS/STUDY POPULATION: Through immunological screening of the *T. muris* stichosome cDNA library and *T. muris* ES macromolecules generated in culture, we identified, cloned, and expressed several vaccine candidates. In ranking these antigens, we selected the most promising recombinant proteins, WAP and CAP-1, and vaccinated AKR mice to evaluate the immunogenicity and efficacy of our candidate. In addition, we collected 240 serum samples in the *T. trichiura* endemic region of Honduras to measure the recognition of WAP and CAP-1 in naturally infected human. RESULTS/ANTICIPATED RESULTS: We measured a statistically significant reduction in larval worm burden in WAP and ES vaccinated mice, but not CAP-1, by microscopy and real-time PCR of *T. muris* DNA. We found a significant relationship between antigen-specific IgG1:IgG2a ratio in the mouse serum and degree of protection. Mouse splenocytes, vaccine-sensitized draining lymph nodes, and mesenteric lymph nodes were antigen-stimulated and their secreted Th1, Th2, and Th17 cytokines were measured by Luminex®. Stimulated mouse lymphoid cells were further analysed for T helper, T cytotoxic, and central/effector memory T cells by Flow Cytometry. Human IgG1, IgG2, and IgE antibody titers against WAP and CAP-1 were measured by ELISA. DISCUSSION/SIGNIFICANCE OF IMPACT: In our study, we describe the T cell dependent mechanism of humoral immunity of 2 promising ES-derived vaccines recombinant proteins, WAP and CAP-1. We evaluated the immune response, indicating a driving a Th2-induced humoral response necessary for protection. We further predict protection and allergenicity of WAP in humans using serum from a cohort in an *T. trichiura* endemic region.

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The effects of autoimmune inflammation on proliferation, differentiation, and androgen receptor signaling in adult prostate stem cells

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OBJECTIVES/SPECIFIC AIMS: The primary goal of this project is to verify murine findings in the human setting. METHODS/STUDY POPULATION: The methods include primary cell isolation and culture, FACS, adoptive transfer, 3D-cell culture, histology, immunofluorescence, xenograft, and tissue recombination. The study population includes patients undergoing radical prostatectomy due to hyperplasia or adjacent bladder or prostate cancer. RESULTS/ANTICIPATED RESULTS: Having verified similar sensitivities to androgen receptor (AR) inhibitors between naive murine and human basal prostate stem cells, we anticipate that autoimmune inflammation in humans affects the response of basal prostate stem cells in a manner similar to the murine setting as well. This includes increased proliferation, differentiation, and response to AR inhibitors. DISCUSSION/SIGNIFICANCE OF IMPACT: The identification of survival mechanisms used by basal prostate stem cells in an androgen deprived environment may give insight to the process by which prostate cancer becomes androgen independent. The effect of inflammation on proliferation, survival, and AR signaling in these cells may also provide information relevant to cancer initiation and progression.

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Temperature regulating wheelchair cushion for prevention of pressure ulcers

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OBJECTIVES/SPECIFIC AIMS: According to the US census, there are 3.3 million Americans who have to use wheelchairs in order to maintain their mobility. About 50% of these patients develop a pressure ulcer at some point during their life time. Three major factors contribute to pressure ulceration; pressure, tissue temperature, and maceration due to sweating. The objective of this study is to develop a temperature regulating wheelchair cushion in order to address elevated tissue temperatures and related sweating. METHODS/STUDY POPULATION: We instrumented a wheelchair with cooling elements, a water filled cushion and a pump. The pump moves the water through the cooling elements where water temperature drops down to 15°C. The water then moves to the cushion where it cools the tissue and then back to the cooling elements. RESULTS/ANTICIPATED RESULTS: We recruited 1 healthy subject to sit on the instrumented wheelchair and then obtained thermographs of the cushion surface using an infrared thermal camera. After 1 minute of sitting on the cushion the minimum temperature was recorded as 27°C. After 10 minutes the temperature dropped to 23.3°C. DISCUSSION/SIGNIFICANCE OF IMPACT: In this ongoing proof-of-concept study we are investigating if circulating chilled water inside a wheelchair cushion is a feasible method to regulate tissue temperatures at the 25–28°C range. This range has been shown to delay ulceration under loading conditions that simulate sitting on a wheelchair. Initial results indicate that this may be an effective ulcer prevention method.

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Dietary fat stimulates growth of pancreatic cancer growth through the cholecystokinin receptor

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OBJECTIVES/SPECIFIC AIMS: Epidemiologic studies have found that the incidence of pancreatic cancer is greatest in countries that consume diets high

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