OBJECTIVES/SPECIFIC AIMS: Treatment of acute myeloid leukemia (AML) is challenging, as apoptosis-resistant AML cells often persist within the bone marrow microenvironment despite chemotherapy. The overall goal of our laboratory is to identify and ultimately target the bone marrow factors that protect AML cells.

METHODS/STUDY POPULATION: Using cell cultures, we previously reported that SDF-1 (CXCL12), an abundant bone marrow chemokine, induces apoptosis of isolated CXCR4+ AML cells, including freshly isolated bone marrow-derived AML cells from approximately one-third of AML patients. However, co-culture of AML cells with differentiating osteoblasts protected AML cells from apoptosis. RESULTS/ANTICIPATED RESULTS: Histone deacetylase inhibitors (HDACi) abrogated the ability of osteoblasts to protect AML cells and altered expression of matrix mineralization genes including tissue nonspecific alkaline phosphatase (TNAP). A different drug, cyclosporine A (CSA), similarly inhibited osteoblast-mediated protection of AML cells and reduced TNAP expression. Specifically targeting osteoblast TNAP via siRNA was sufficient to prevent osteoblasts from protecting AML cells in co-cultures. In addition, we are targeting TNAP enzymatically.

DISCUSSION/SIGNIFICANCE OF IMPACT: Our results indicate that targeting TNAP may be useful in AML treatment to render the bone marrow microenvironment more hostile to leukemic cell survival.

Sexual dimorphism in a mouse model of syndromic thoracic aortic aneurysm
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OBJECTIVES/SPECIFIC AIMS: Pre-clinical and clinical observations have noted that increased aortic dilation is associated with male sex. Using an experimental model of severe, syndromic thoracic aortic aneurysms, we quantify aortic dilation and elastin stability in male versus female mice.

METHODS/STUDY POPULATION: Ascending aortas from male and female FBN1-/-mR/mR mice and their wild type littermates were assessed every 4 weeks from 6 to 18 weeks of age by ultrasound. Measurements were taken luminal edge to luminal edge in diastole. At termination, aortas were harvested for RT-PCR analysis of extracellular matrix genes. Aortas were serially sectioned and elastin fragmentation was imaged by auto-fluorescence.

RESULTS/ANTICIPATED RESULTS: At 12 weeks of age, differences of aortic diameters between male and female FBN1-/-mR/mR mice were significantly different (2.24 ± 0.43 vs. 1.57 ± 0.22 mm; p = 0.002). There were no significant differences between sexes of wild type littermates (1.29 ± 0.13 vs. 1.23 ± 0.08 mm; p = 0.71). Male sex was associated with increased elastin but not fibrillin-1 mRNA expression. Ascending aortas from male and female FBN1-/-mR/mR mice significantly differed in the degree of elastin fragmentation (2.76 vs. 1.85 breaks/100 µm aorta; p = 0.03).

DISCUSSION/SIGNIFICANCE OF IMPACT: Sexual dimorphism of thoracic aortic dilation observed in human TAA patients was recapitulated in the fibrillin-1 hypomorphic mouse model of syndromic thoracic aortic aneurysms. Differences in this mouse model could be explained by the differential expression of extracellular matrix genes.

Sodium-glucose transporter 2 is a novel diagnostic and therapeutic target for early-stage lung adenocarcinoma
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OBJECTIVES/SPECIFIC AIMS: Lung cancer claims 160,000 lives in the United States every year, and lung adenocarcinoma (LADC) is the most frequent type. Early diagnosis is crucial. Computed tomography (CT) is very sensitive in identifying early-stage lung nodules, but has low specificity. Increased glucose uptake is a hallmark of cancer measurable in vivo by fluorodeoxyglucose (FDG) positron-emission tomography (PET). FDG PET is widely used for cancer staging but has low sensitivity in the diagnosis of solitary lung nodules. We have previously identified an alternative glucose transporter, SGLT2, expressed in different types of cancer but not detected by FDG PET. SGLT2 activity can be measured in vivo with 2-deoxy-2-fluoro-D-glucose (FDG-FDG). The objective of this study was to test the hypothesis that SGLT2 is a novel diagnostic and therapeutic target in FDG-negative, early stage LADC.

METHODS/STUDY POPULATION: To study glucose transporter expression in LADC, we performed immunohistochemistry with SGLT2- and GLUT1-specific antibodies in human lung pre-malignant lesions and LADC samples. To verify the possibility of detecting SGLT2 activity in vivo, we performed microPET imaging with the SGLT-specific tracer Me4FDG in a Kras-driven, p53-null genetically engineered mouse model and in patient-derived xenografts.