Objective
Cancer typically arises from mutations which lead to uncontrolled cell proliferation, and culminates in invasion of adjacent tissues and metastatic dissemination to distant organs. Such ectopic behaviour usually results in increased reactive oxygen species (ROS) as a consequence of heightened energy requirements and/or stress from distinct microenvironments during metastasis. Although many malignant cells die of ROS toxicity, cells which can adapt and maintain redox homeostasis have a high potential for metastatic development. Our research on oxidative stress in Ewing and osteosarcoma aims to identify key stress-adaptation mechanisms of therapeutic potential.

Results
Oxidative stress is known to induce stress granules (SGs), which are cytoplasmic aggregates of RNA and RNA binding proteins. We found SG formation to be a novel protective mechanism, whereby the sequestered mRNAs are translationally silenced, allowing for selective translational-enhancement of cytoprotective proteins, including Nrf2—the master antioxidant response regulator. We then performed drug screens followed by immunofluorescence and immunoblotting, and found that MS-275 potently inhibits SG formation, decreases Nrf2 induction, increases ROS, and enhances apoptosis under stress, without affecting cell proliferation in ambient conditions. In mice bearing sarcoma xenografts, MS-275 blocked local sarcoma invasion, and dramatically inhibited lung metastases.

Conclusion
These data suggest an exciting new strategy to target metastatic development through SG inhibition, which reduces the adaptive capacity of sarcoma cells to oxidative stress. As oxidative stress is also implicated in neurodegenerative, cardiovascular, and metabolic illnesses, further elucidation of adaptation mechanisms to ROS can have widespread impacts on treating cancers and a diversity of additional diseases.

Themes:
Check (highlight) the most applicable theme according to the abstract.

| Innovation and Technology | Health and Wellness | Culture and Society | Sustainability and Conservation |

Comments: Concise, well-written abstract. Flows logically and easy to comprehend. All the best at MURC!