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Commentary: A Special Edition in bone sarcoma

Joseph A Ludwig [a,*], Brian Van Tine [b]

[a] The University of Texas MD Anderson Cancer Center, USA
[b] Washington University, USA

As a multidisciplinary peer-reviewed specialty journal focused on cancer-induced bone diseases, the Journal of Bone Oncology features various articles related to the bone tumor microenvironment, imaging, bone-targeted therapies, skeletal complications (and their corrective surgical options), and bone metastases. In this Special Edition dedicated to primary bone cancers—chiefly Ewing sarcoma (ES), chondrosarcoma (CS), and osteosarcoma (OS)—the authors feature novel preclinical models that shed new light on bone tumor biology, provide fresh insights into molecular targets and potential therapies, and advance the current state-of-the-art surgical management.

From a basic science perspective, Munoz-Garcia et al. underscore the critical role the tumor microenvironment (TME), extracellular matrix, and biomechanical forces have in regulating bone sarcoma behavior (page XXX). In contrast to traditional two-dimensional cell culture systems that fail to recapitulate the physiological cues experienced by tumor cells in vivo, the authors describe the recent popularity of natural and bioengineered 3D culture methods that are used to mimic the osseous tumor microenvironment. Within these lab-based 'bioengineered tumors,' cancer cells often better resemble their human tumor counterparts, thereby facilitating a more accurate estimate of drug response, resistance mechanisms, and differentiation capacity. Chang et al. expand upon the importance of the TME by highlighting the complex, potentially druggable, bidirectional relationship that mesenchymal stem cells (MSCs) have with OS (page XXX).

Continuing this osteosarcoma focus, Smrke et al. address the successes and failures of using immunotherapy to harness the patient's immune response (page XXX). While mifamurtide has shown modest antineoplastic activity by activating tumor-associated macrophages, the checkpoint inhibitors have not yielded the promising results that one might have expected for a sarcoma subtype rich in mutations and copy number alterations. Given the genetic complexity of these tumors and marked inter-patient heterogeneity, it remains to be seen whether CAR-T cells and other patient-specific therapies will eventually prove useful. Taking an alternative approach for osteosarcoma treatment (page XXX), Zhao et al. describe how ferroptosis—regulated cell death characterized by an iron-dependent accumulation of lipid reactive oxygen species—may prove useful.

In their in-depth review of Ewing sarcoma, the second-most common pediatric bone sarcoma, Flores and Grohar concisely summarize the oncogenic effects of the pathognomonic EWS-FLI1 fusion protein while describing the challenges associated with its direct and indirect targeting (page XXX). In the absence of known EWS-FLI1 antagonists, they outline a wide range of potential anti-cancer strategies that can impair EWS-FLI1 expression or mitigate its impact upon downstream epigenetic targets.

With an emphasis on therapeutic applications relevant to all bone sarcomas, Truong et al. provide a comprehensive review of the IGF/PI3K/mTOR and YAP/TAZ pathway inhibitors undergoing clinical investigation (page XXX). Finally, given the significant effect on patients' quality of life and outcomes, Fijiwara et al. compare the results of endoprosthetic replacement and autograft reconstruction outcomes in patients undergoing limb-salvage peri-acetabular tumor resections (page XXX). They additionally highlight innovative techniques using computer-aided navigation to achieve superior functional outcomes.

Taken all together, advances are occurring on multiple fronts in osteosarcoma, Ewing's and chondrosarcoma. It is our hope that this collection of manuscripts will highlight current research and spawn new pursuits for the treatment of bone tumors.

Abbreviations: (CS), chondrosarcoma; (OS), osteosarcoma; (ES), Ewing sarcoma.

* Corresponding author.
E-mail address: jaludwig@mdanderson.org (J.A. Ludwig).

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