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Short Communication
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Lessons from Targeting the Endothelin Axis in Myeloma and Prostate Cancer

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Endothelin (ET) and other neuropeptides are potent mitogens for both benign and malignant cells through G-protein receptor binding and signal transduction [1]. Aberrant expression of several components of the endothelin axis, including Endothelin (ET) and its receptors, ET-A and ETB is found in different tumors types, including Prostate Cancer (PC) [1]. Evidence of increased paracrine and autocrine signaling through the endothelin axis in PC cells has triggered clinical testing of endothelin receptor inhibitors. However, lack of clinical benefit has prevented further development of this approach [2-5]. At the cellular level, we previously reported ET-induced upregulation of proteasome activity and associated proliferative and antiapoptotic effects in androgen-independent PC cells [6]. These effects were reversed with the use of the proteasome inhibitor bortezomib [7]. However, bortezomib failed to demonstrate clinical activity in prostate cancer patients, therefore its clinical use for inhibiting the endothelin axis could not be supported in that setting [8-11].

Nevertheless, in Multiple Myeloma (MM) bortezomib is a very active drug and often consists the backbone for most myeloma treatment regimens [12-14]. We have previously revealed the over expression of ET-B in MM mediating resistance to bortezomib via upregulation of proteasome activity and resultant MAPK pathway activation [15].

In their recent work, published in the British Journal of Haematology, Russignan et al [16]. further complemented these findings by reporting ET-B over expression in human malignant plasma cells compared to healthy donors. Moreover, the addition of an ET receptor antagonist to bortezomib enhanced the cytotoxic effect on myeloma cells [15,16].

In conclusion, the rational for ET receptor antagonism in myeloma has been documented. Therefore, design and conduction of a clinical trial combining bortezomib and a non-selective ET receptor antagonist, for example bosentan, or a selective ETB receptor antagonist, appears to be a reasonable next step and holds promise for further improving outcomes of MM patients.

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