The novel β2-selective proteasome inhibitor LU-102 synergizes with bortezomib and carfilzomib to overcome proteasome inhibitor resistance of myeloma cells.

**Proteolytically active sites**

- approved proteasome-inhibiting drugs: bortezomib, carfilzomib
- bortezomib resistance in myeloma:
  - downregulation of the activation status of the unfolded protein response
  - upregulation of the β2 proteasome activity

**Development of new selective inhibitor**

LU-102

**Proteasome inhibitor-resistant myeloma cells**

- highly synergistic cytotoxic activity via endoplasmatic reticulum stress-induced apoptosis
- prolonged proteasome inhibition
- increased activation of the unfolded protein response
- increased activation of IRE1-α activity

Kraus et al., Haematologica, 2015