

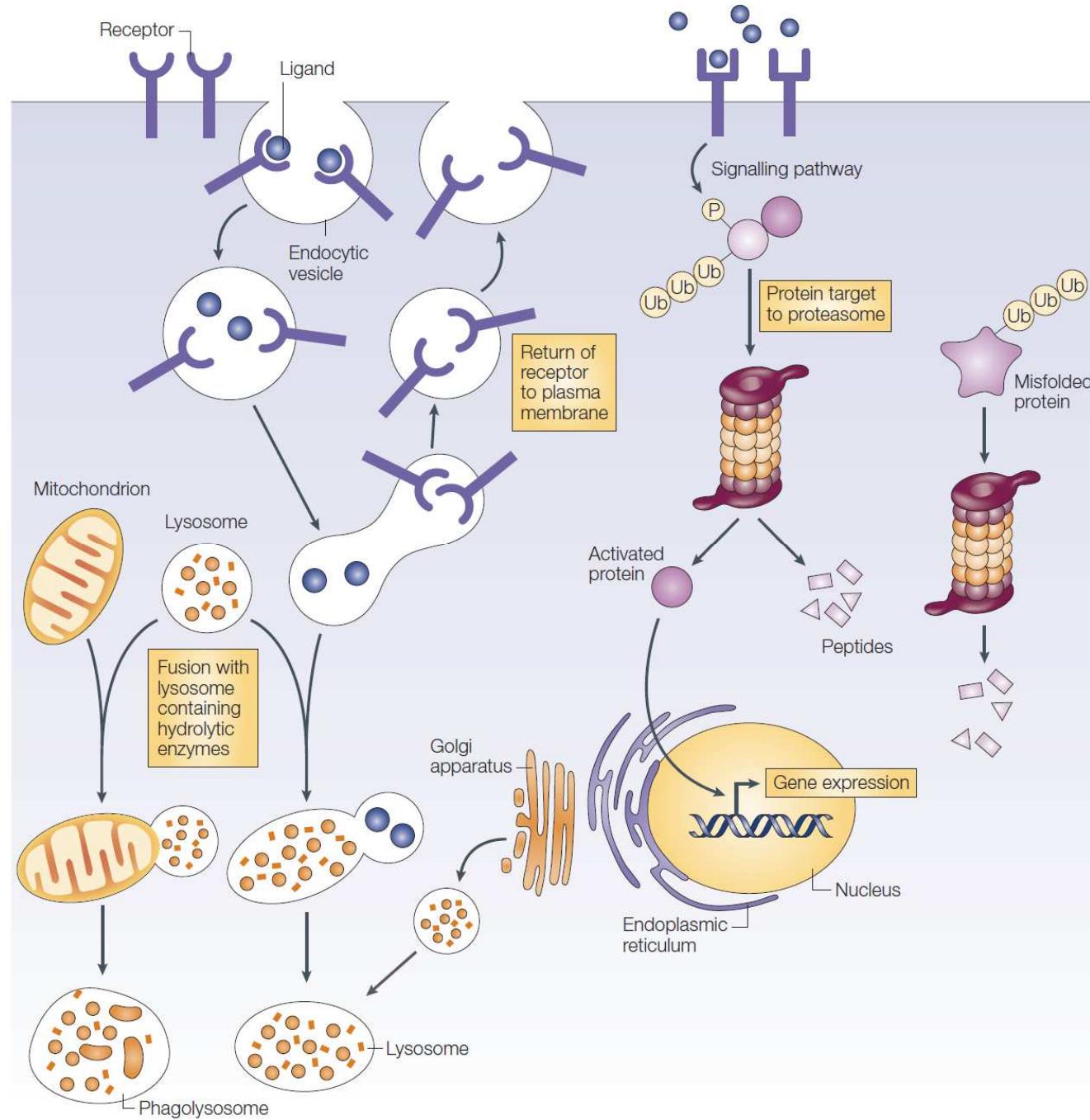


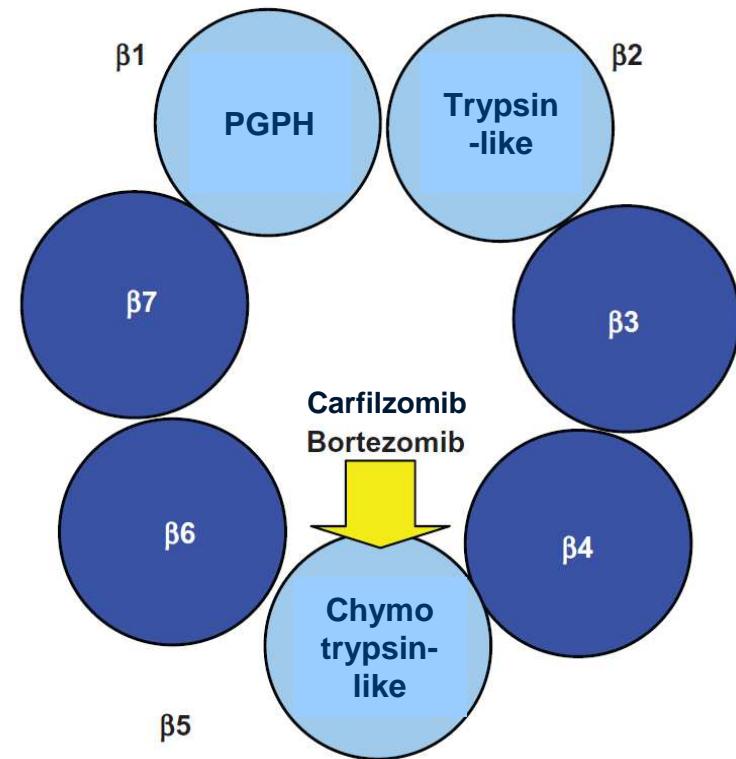
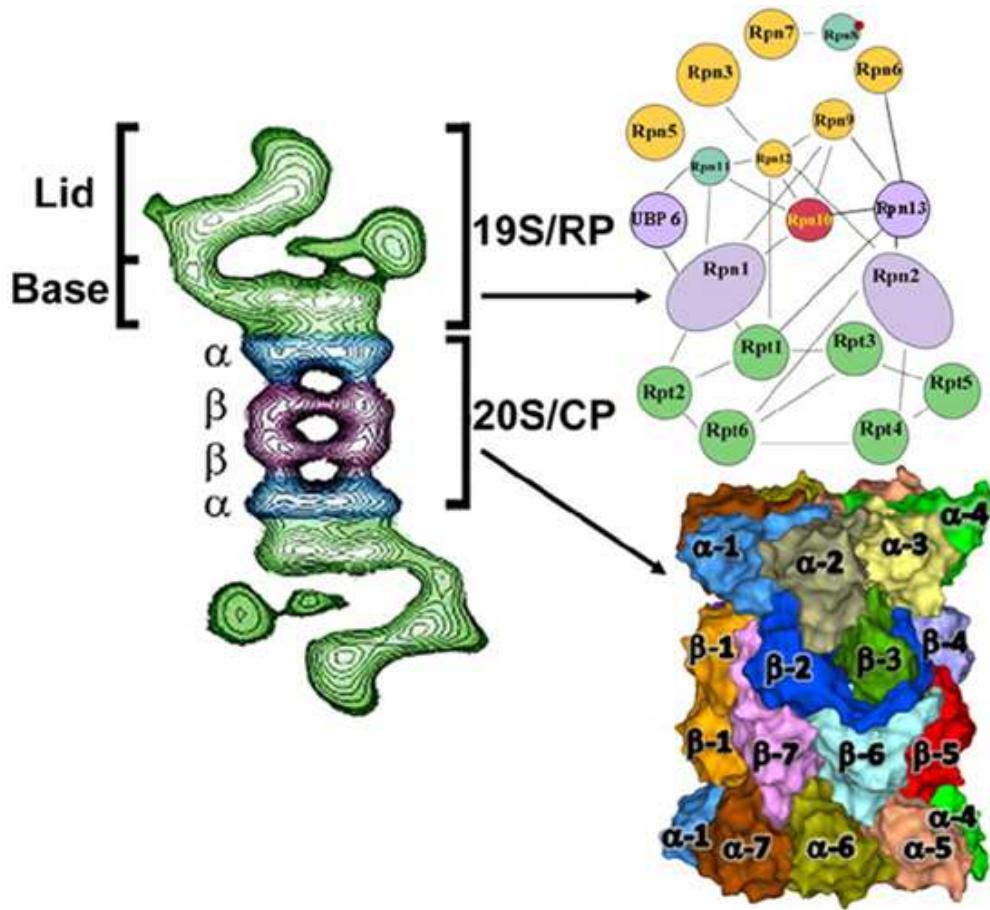
Project BASTION „From Basic to Translational Research in Oncology”

Evaluation of the role of proteostatic mechanisms in tumor development and efficacy of anti-cancer treatment

Dominika Nowis

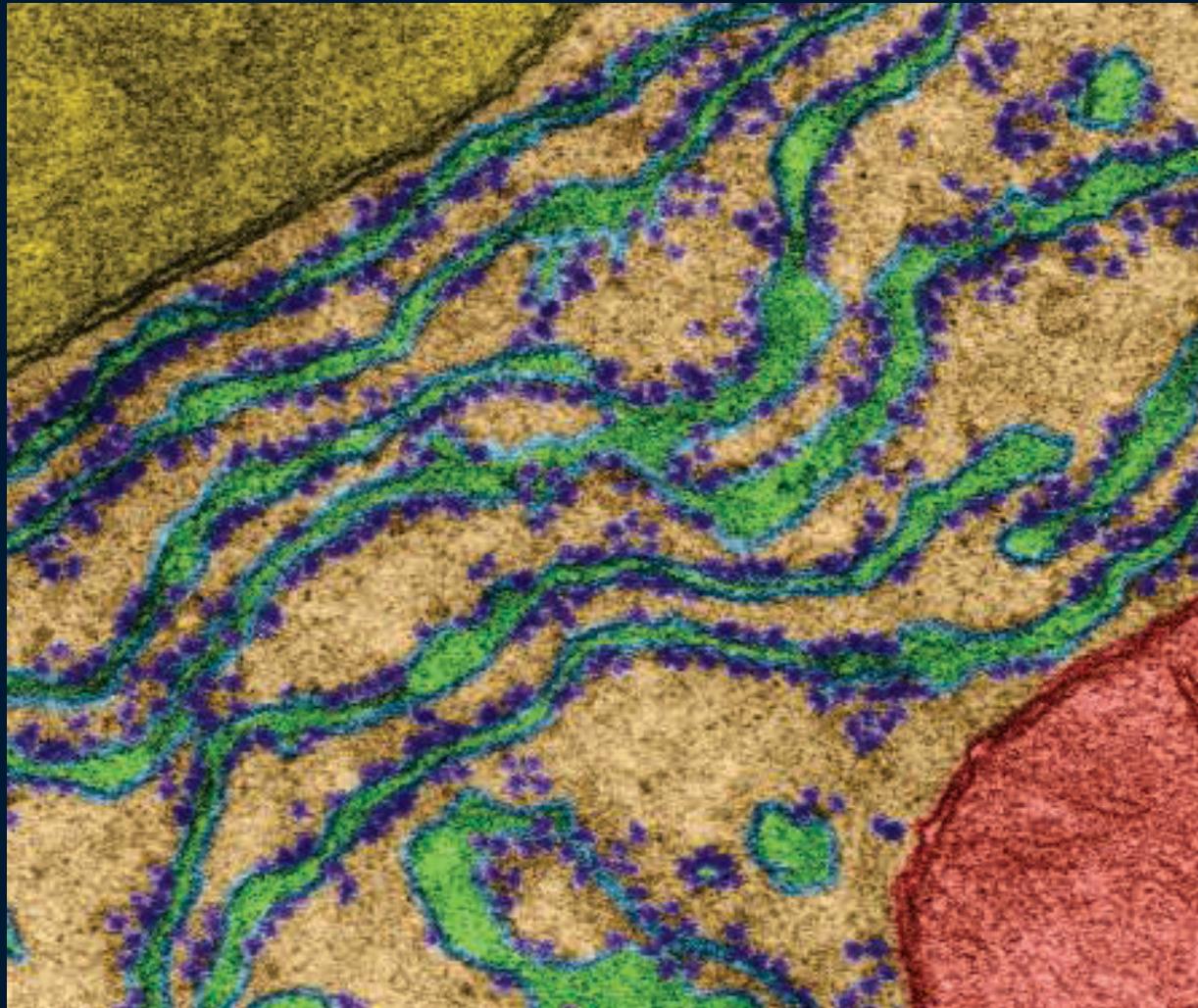


a Lysosome**b Proteasome**



- **Bortezomib (Velcade)**
- **Carfilzomib (Kyprolis)**

Endoplasmic reticulum (ER)



ribosomes
proteins

Marx J. Science 2006; 313:1564.

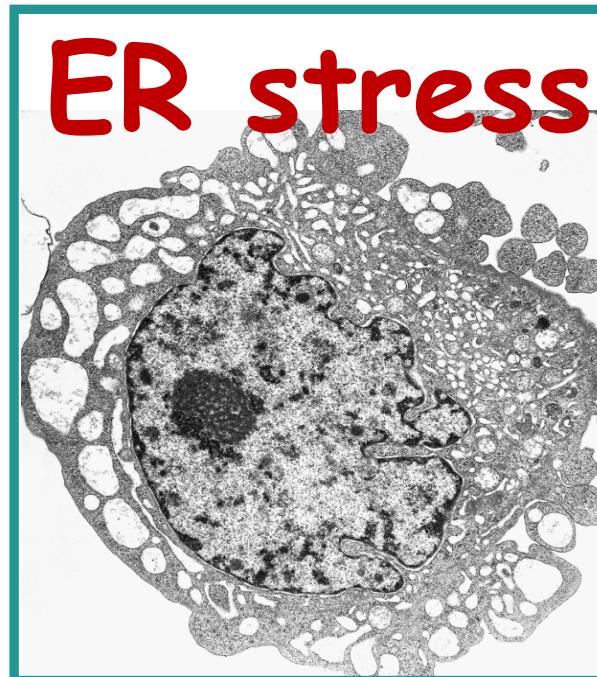
Errors in
posttranslational
protein modifications

Increased
protein synthesis

Changes in
 $[Ca^{2+}]$

Starvation,
lack of energy

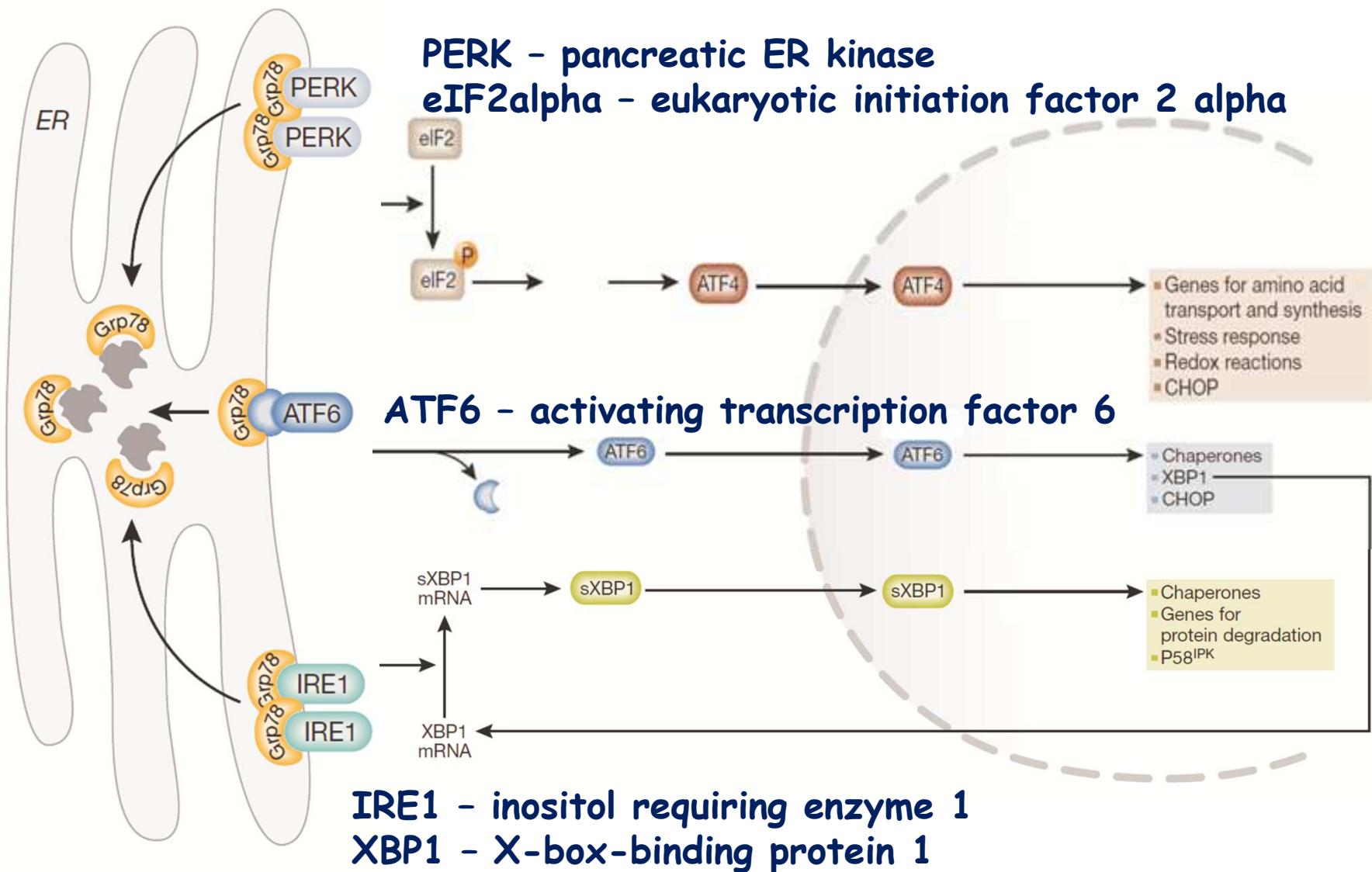
Oxidoreductive
imbalance



UPR - unfolded protein response

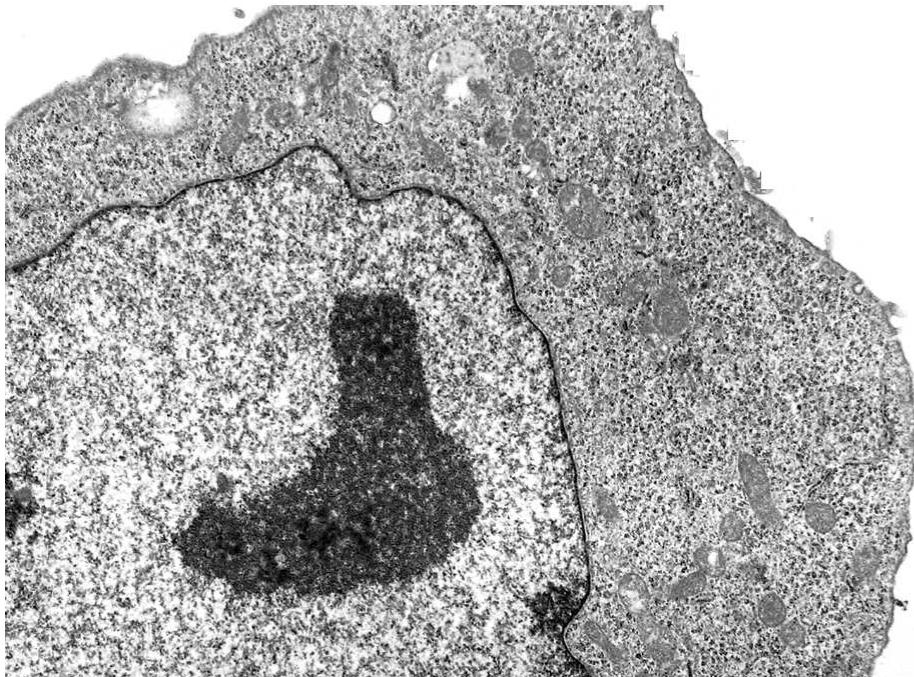
- Global inhibition of mRNA translation and protein synthesis
- Re-folding of misfolded proteins
- Proteasome-mediated ERAD (Endoplasmic Reticulum-associated degradation)
- ER expansion

Three pathways of unfolded protein response (UPR):

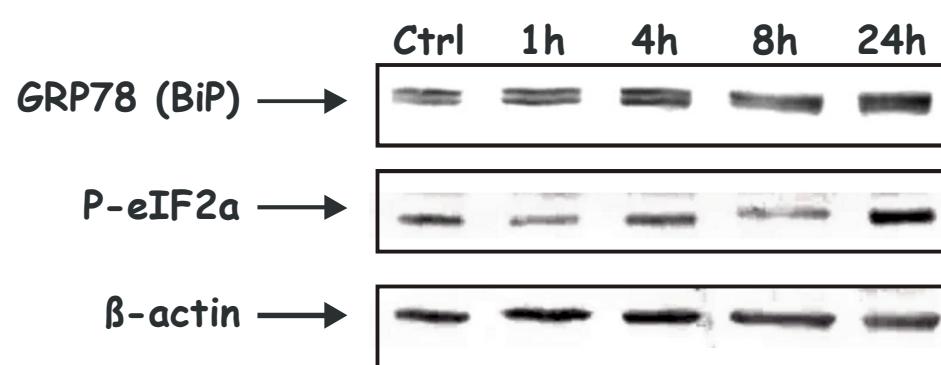
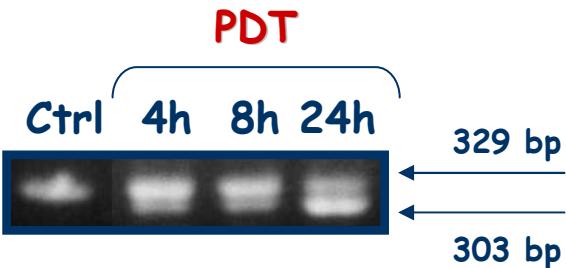
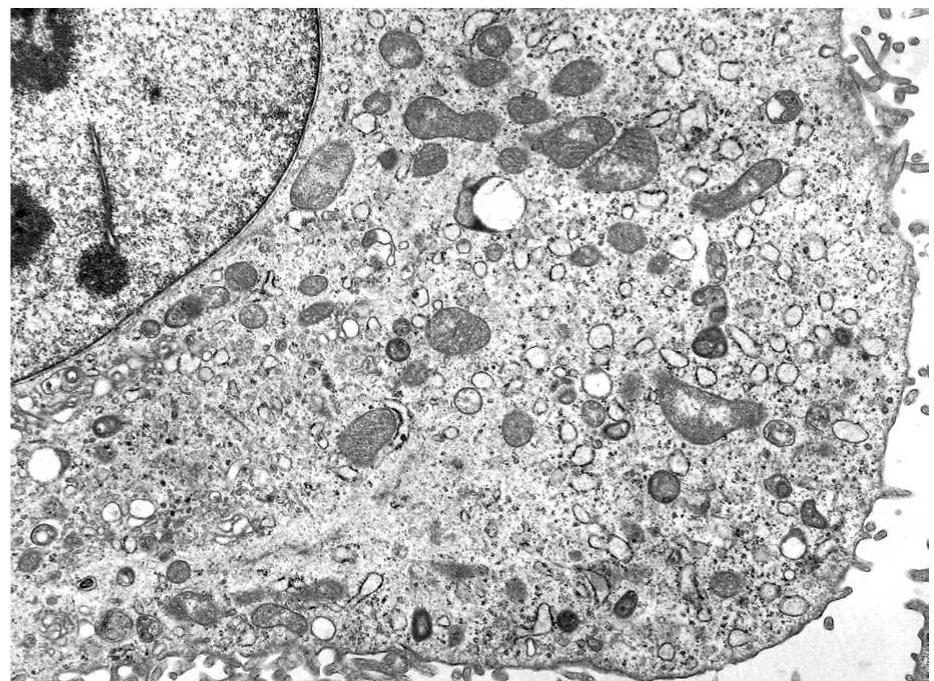


PDT induces ER stress

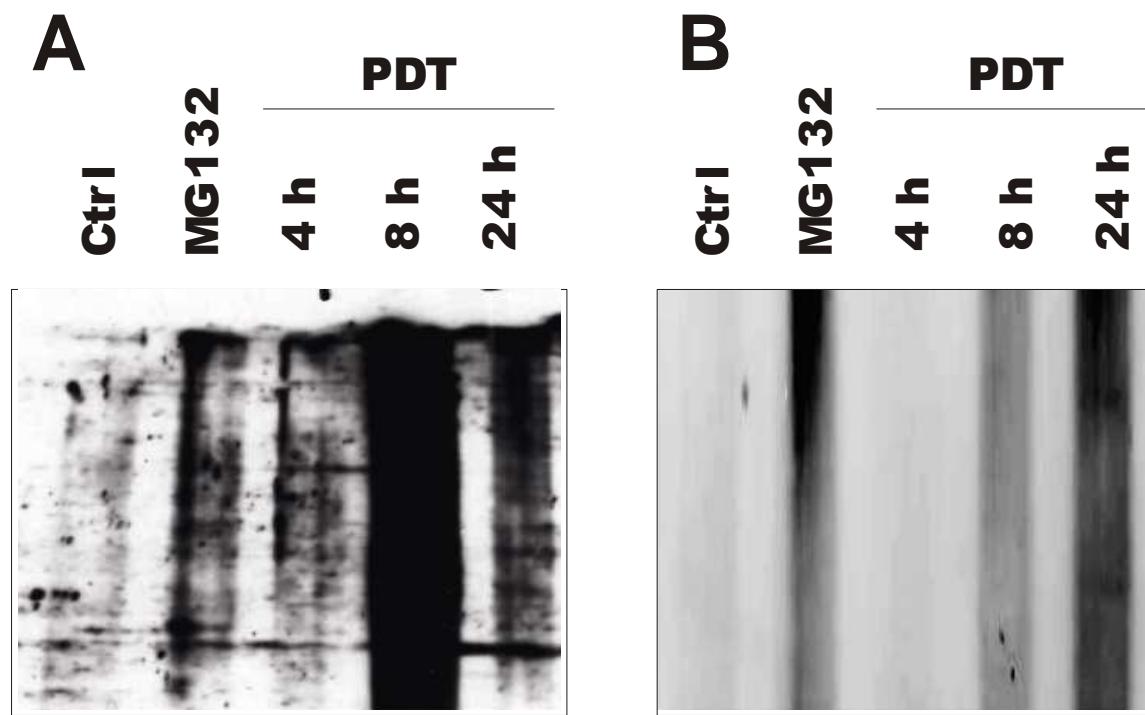
Controls



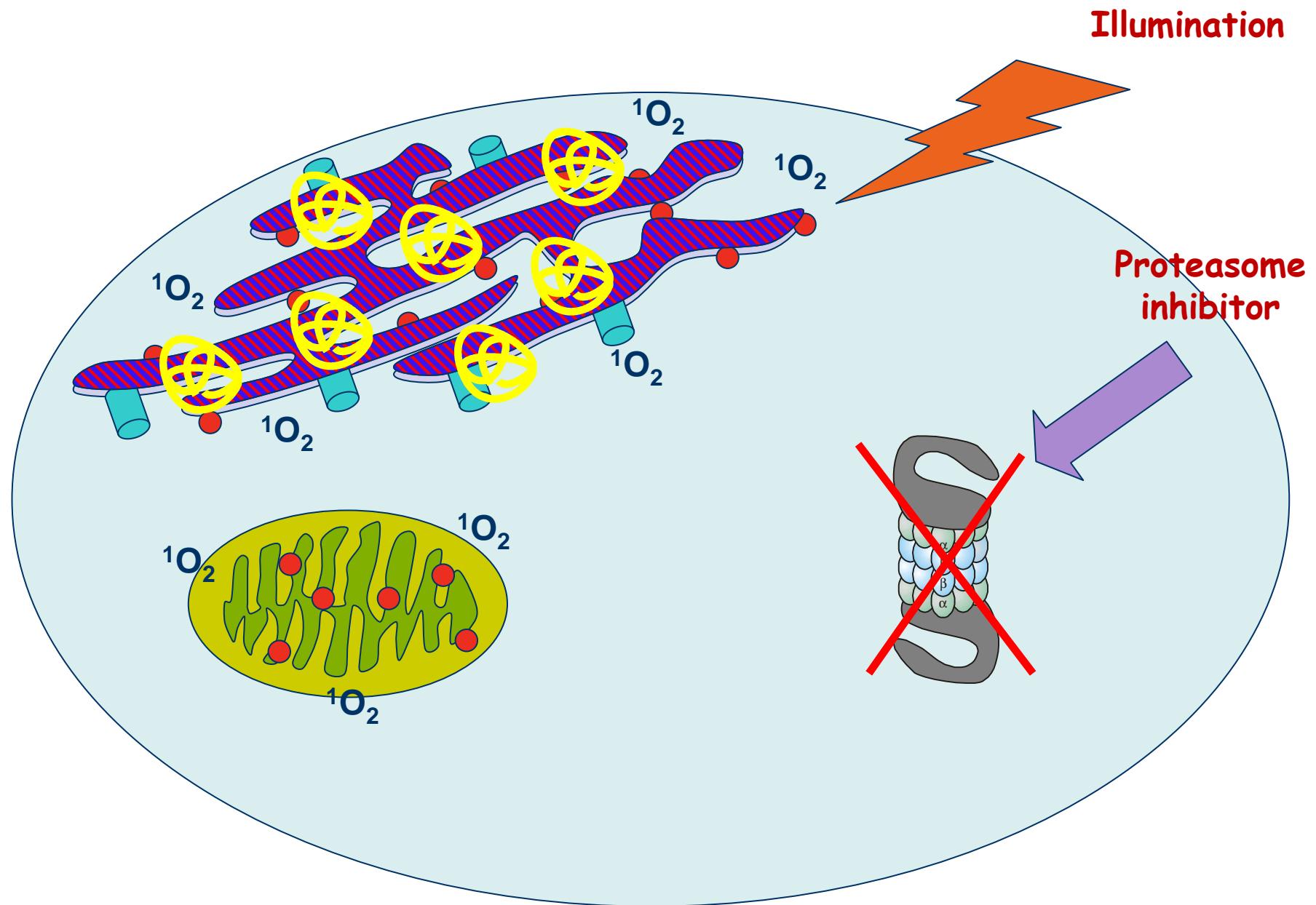
PDT - 24h



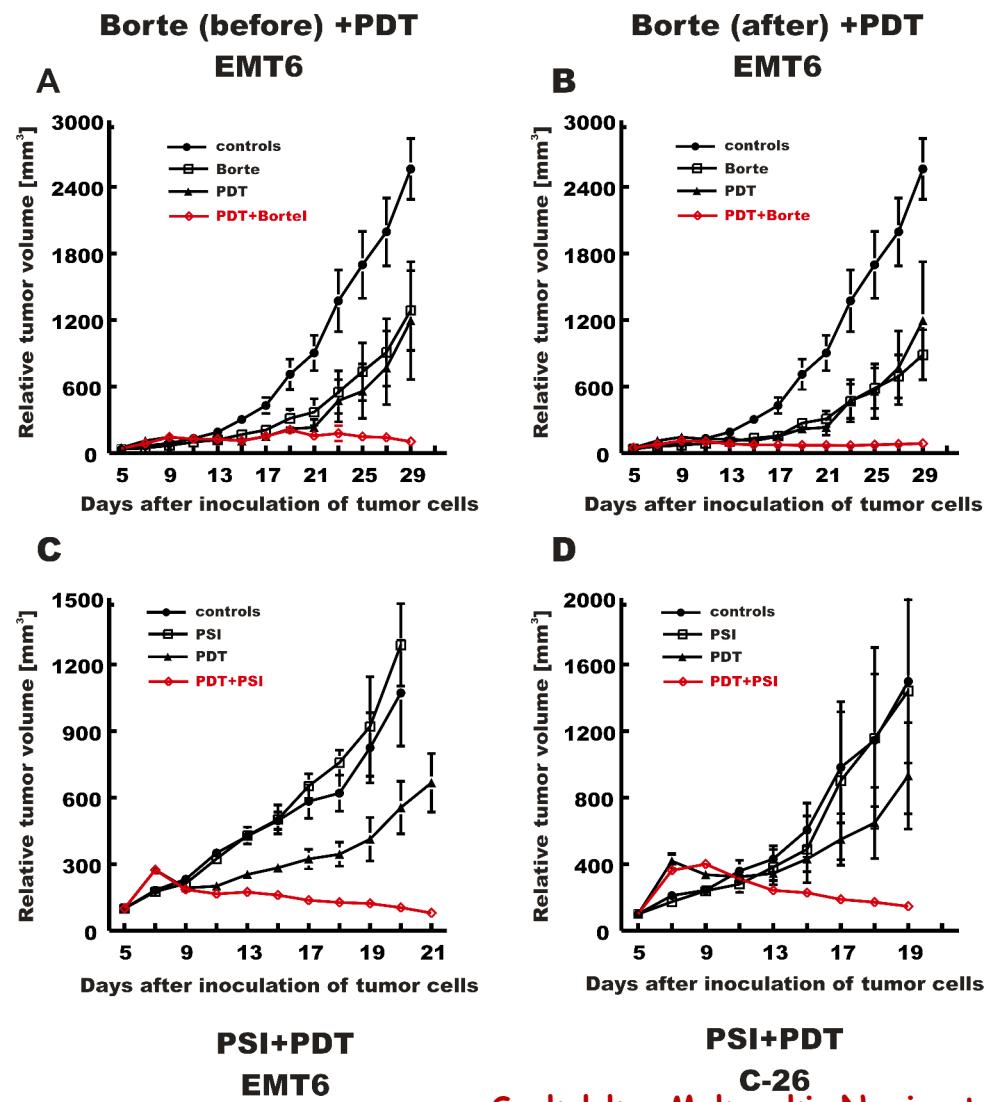
PDT induces carbonylation and polyubiquitination of cellular proteins



HeLa cells
Photofrin 10 µg/ml for 24 h
Light - 2.4 J/cm²

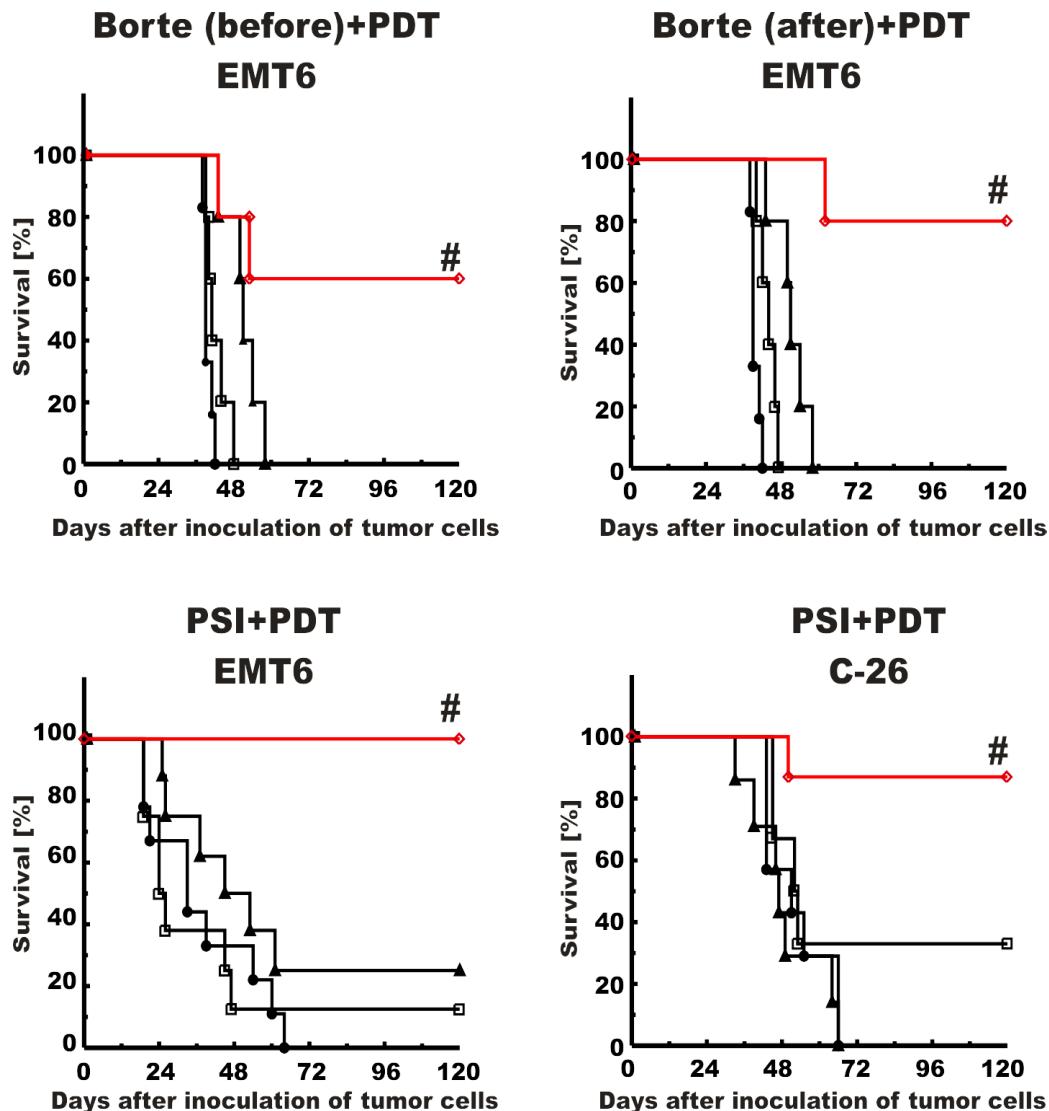


Proteasome inhibition potentiates antitumor effects of PDT *in vivo*



Szokalska, Makowski, Nowis et al., Cancer Res 2009;69:4235

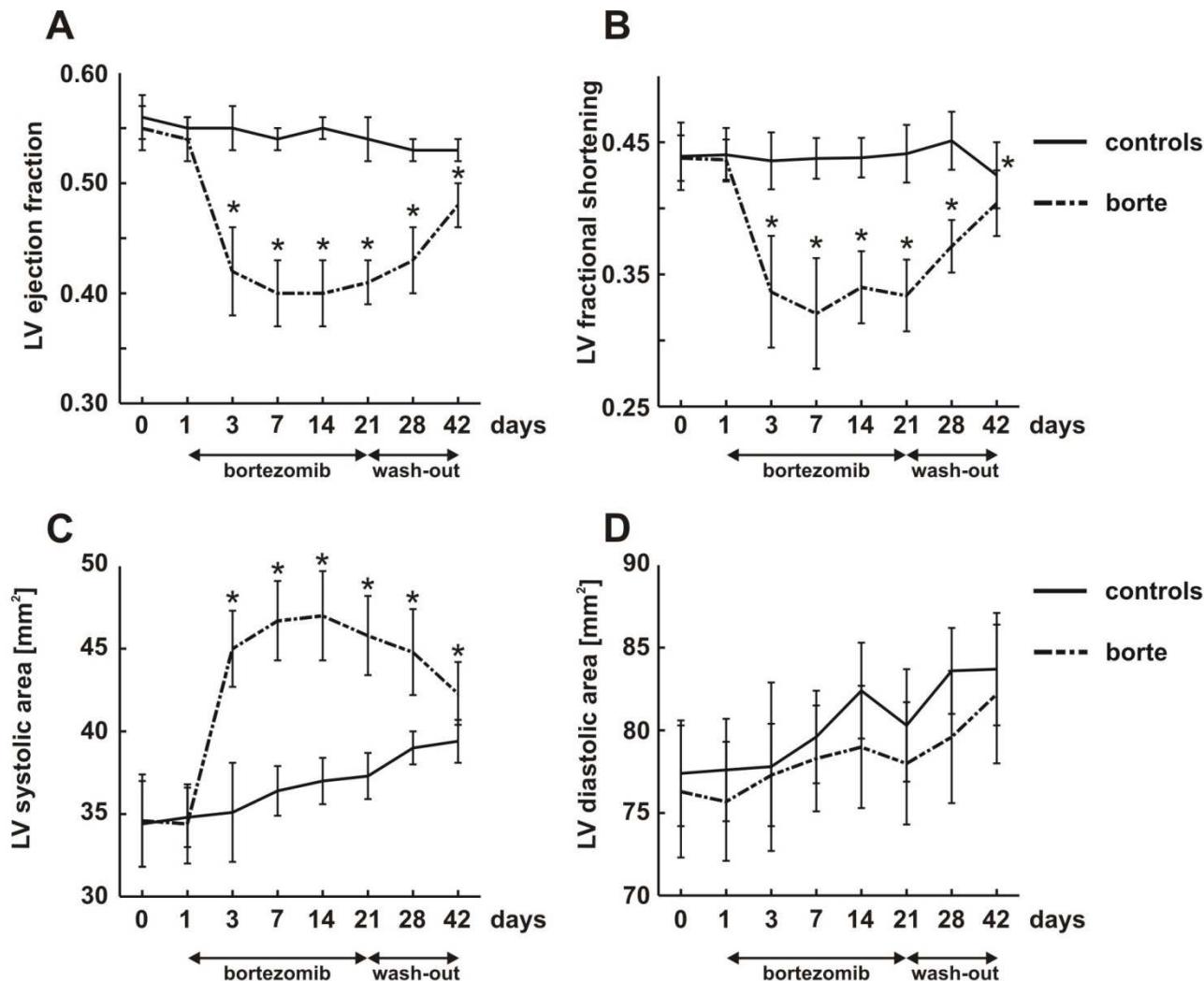
Proteasome inhibition potentiates antitumor effects of PDT *in vivo*



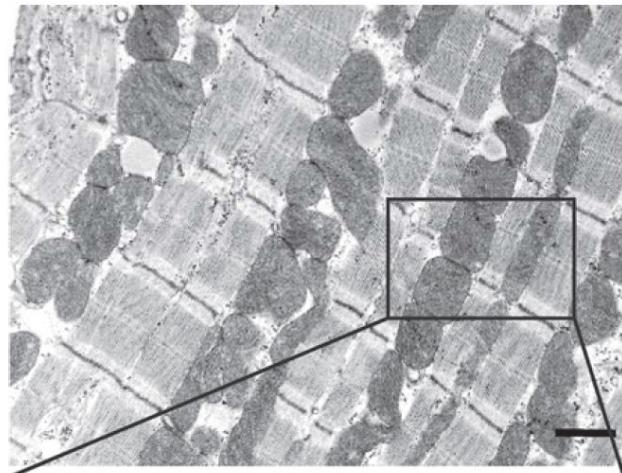
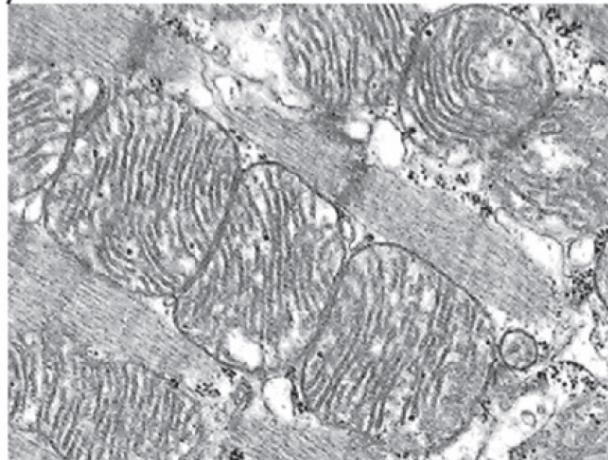
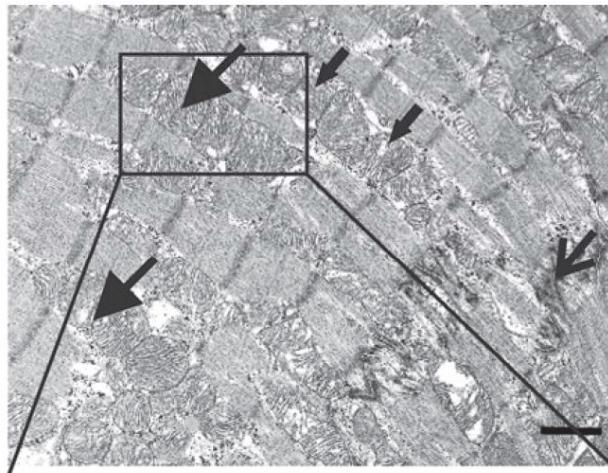
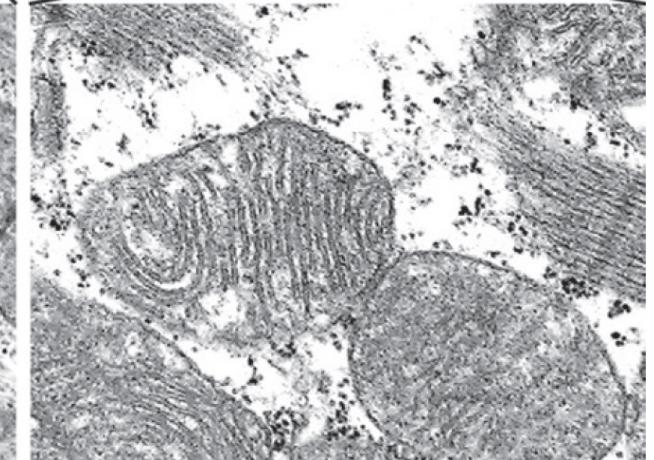
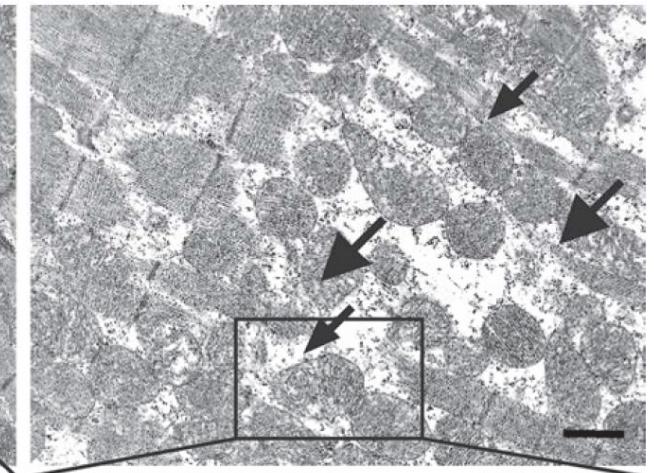
Oxidative stress modifiers in haematological malignancies:

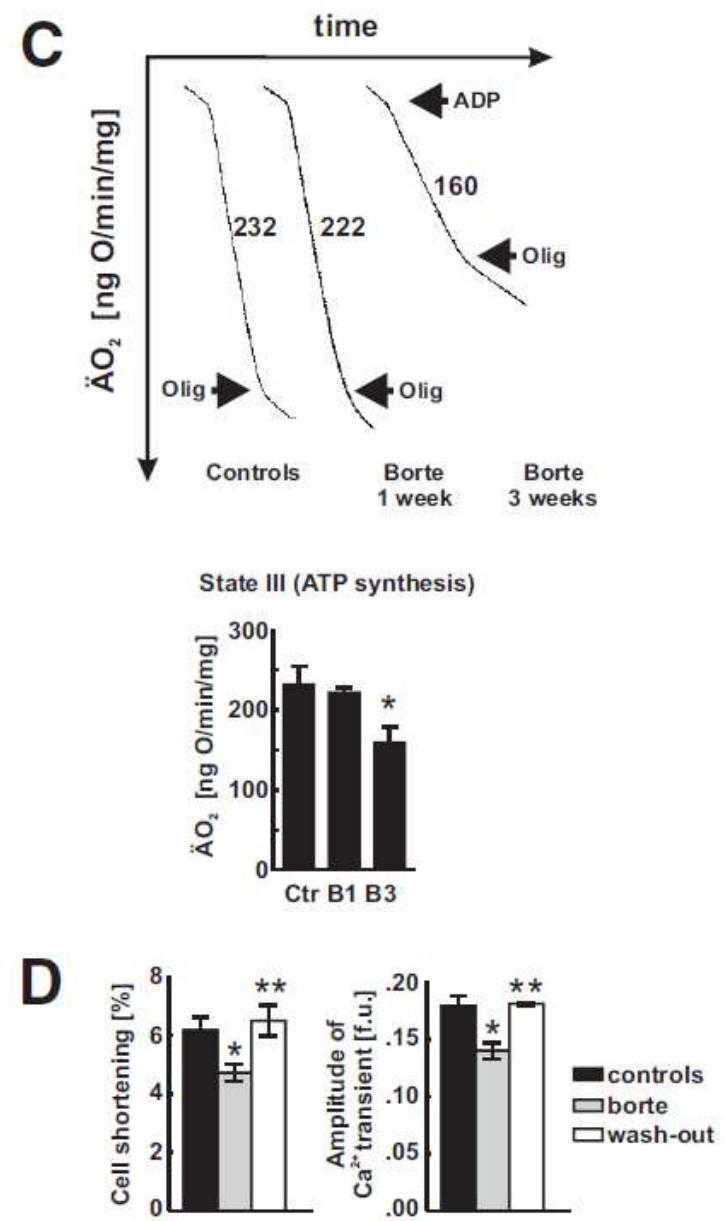
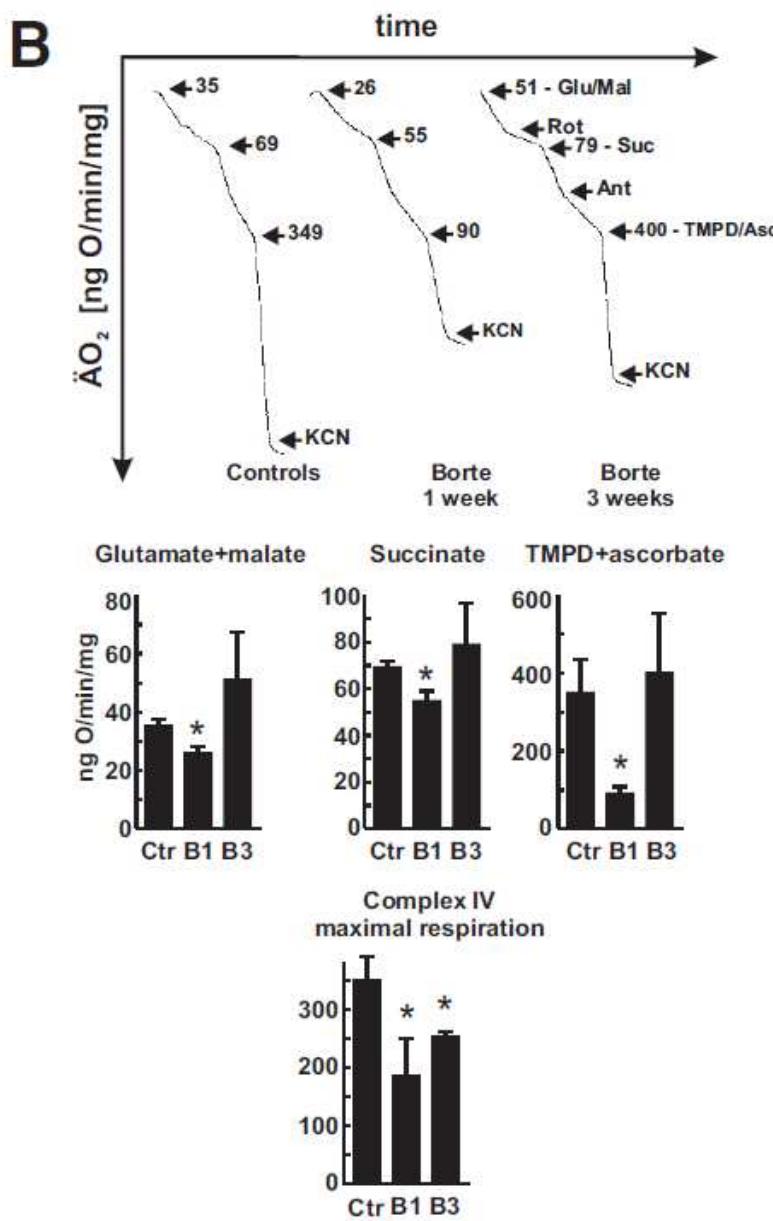
- Thioredoxin / thioredoxin reductase (Trx/TrxR)
 - Protein disulphide isomerase (PDI)
 - Peroxiredoxin family (Prdx)
-
- Multiple myeloma (MM)
 - Acute myeloid leukemia (AML)
 - B-cell lymphomas and leukemias

Bortezomib impairs systolic heart function in rats



Nowis D et al., Am J Pathol. 2010 Jun;176(6):2658-68

A**Controls****borte 1 week****borte 3 weeks**



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