Effect of ABCB1 Multidrug Resistance Protein on Efficacy of Anti-Myeloma Drugs in Carfilzomib-Resistant Myeloma Model

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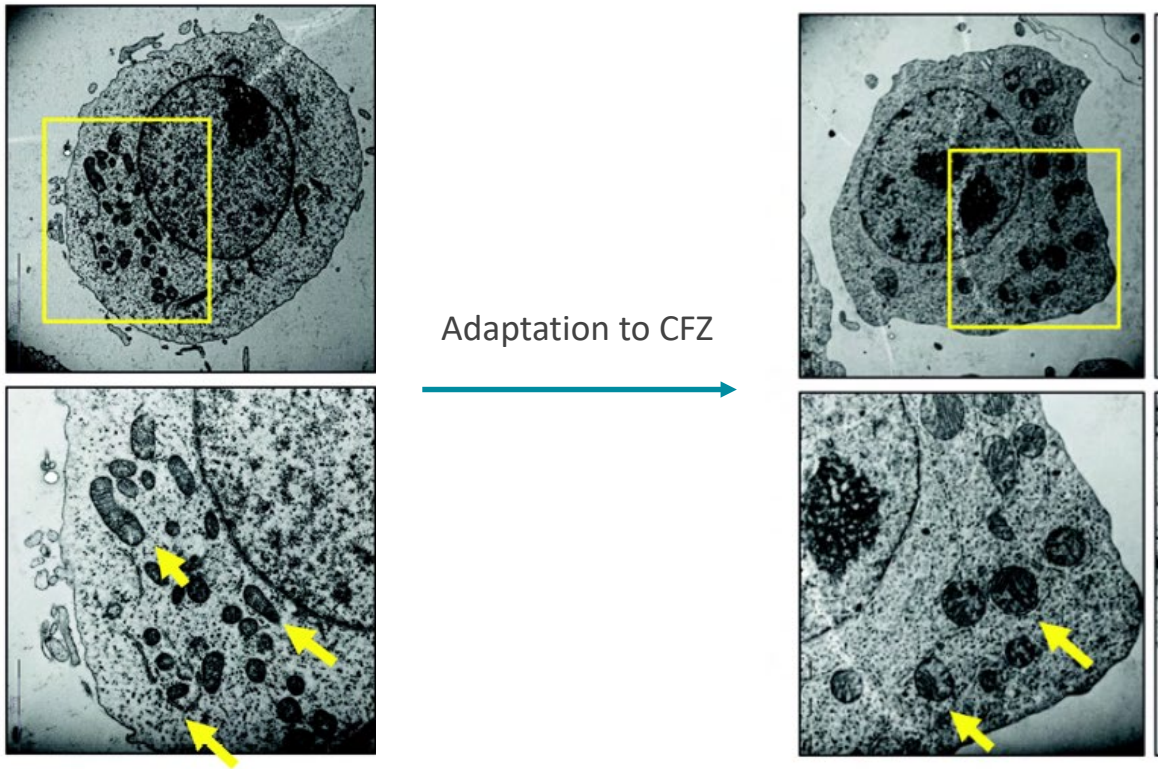
Disclosures

- Konstantin Byrgazov (Oncopeptides AB, employment)
- Ana Slipicevic (Oncopeptides AB, employment)
- Fredrik Lehmann (Oncopeptides AB, employment, equity)
- Christoph Driessen (Oncopeptides AB, research grant)

Resistance to carfilzomib

- Carfilzomib (CFZ) is a second-generation proteasome inhibitor approved for multiple myeloma (MM) treatment in 2012.
- CFZ-resistance is associated with complex metabolic changes and up-regulation of multidrug resistance protein MDR1/ABCB1 (Besse et al., 2018).



Besse et al., Haematologica 2019

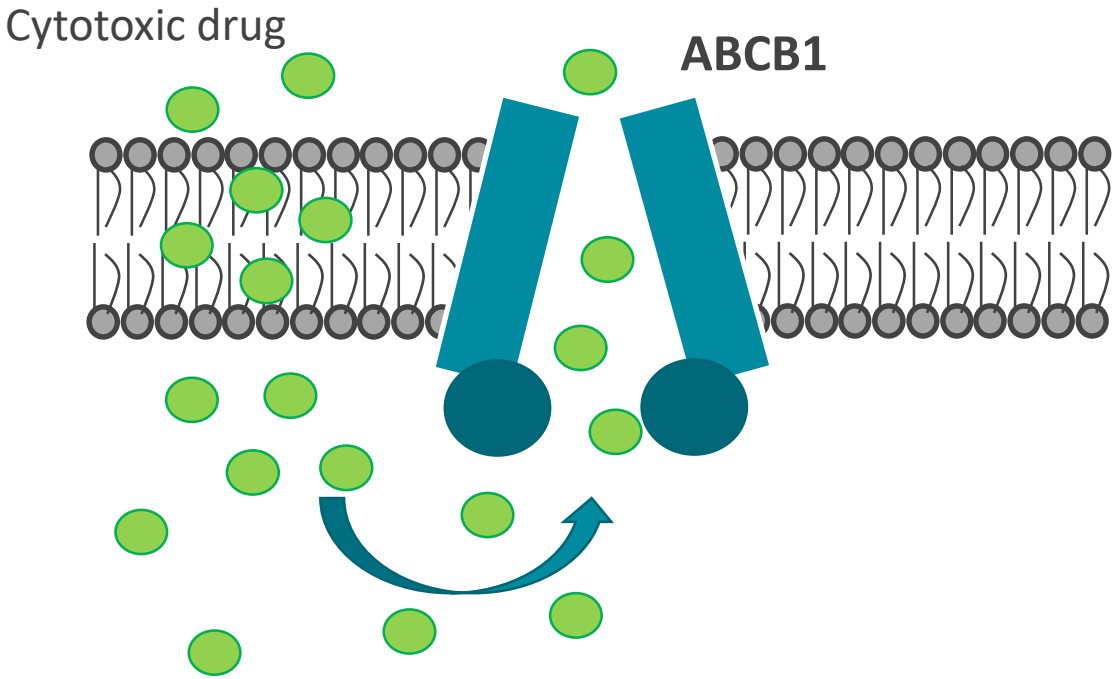
Features of CFZ-resistance

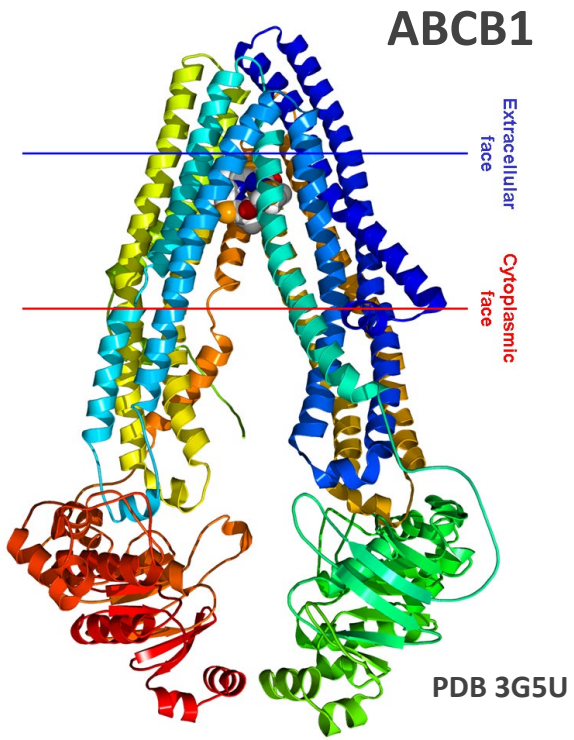
1. Larger Mitochondria
2. Up-regulation of oxidative phosphorylation (OXYPHOS) ↑
3. Independence on standard proteasome activity
4. Multidrug resistance protein ABCB1 is up-regulated ↑

Besse et al., Leukemia 2018
Besse et al., Haematologica 2019

Multidrug resistance protein ABCB1/MDR1

- ABCB1 is an efflux pump removing toxic compounds from the cell.
- Implicated in drug resistance in cancer.
- Prognostic value in myeloma patients treated with VAD (Vincristine, Adriamycin/doxorubicin, dexamethasone) (Grogan et al., Blood 1993).
- Up-regulated in carfilzomib-resistant myeloma and progression to extramedullary disease (EMD) in MM (Besse et al., Leukemia 2018).



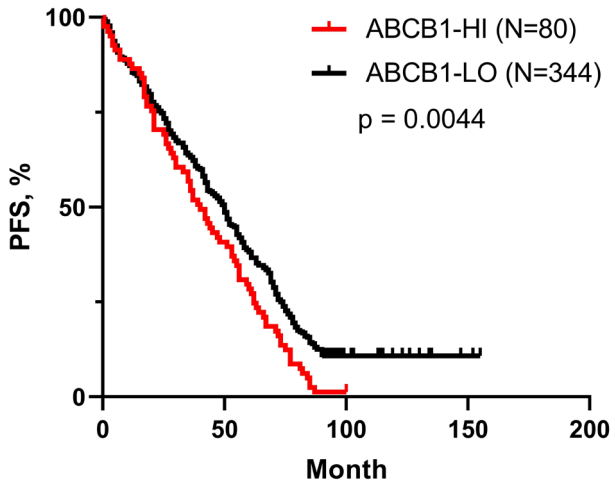


High ABCB1 expression is associated with high-risk myeloma

A) Higher expression of *ABCB1* confers shorter progression-free survival in multiple myeloma patients treated with novel drugs (proteasome inhibitor + immunomodulatory drug), 40 vs 50 month, HR 0.800, 95% CI 0.6255-1.023.

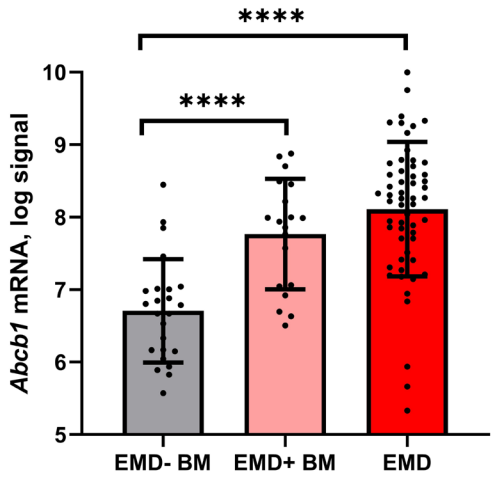
B) *ABCB1* murine homologue *Abcb1* is up-regulated in extra-medullary disease(EMD)-prone MYC-driven mouse model of multiple myeloma.

A



Source: GSE136337

B



****, $p < 0.0001$ U test

Source: GSE111921

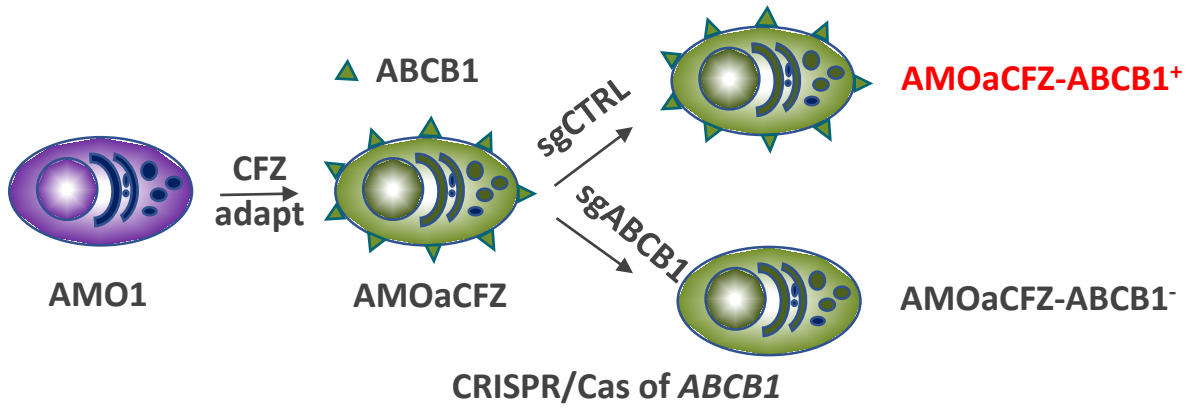
Differential effect of ABCB1 on anti-myeloma drugs in carfilzomib-resistant myeloma model

A) Generation of isogenic pair of carfilzomib-resistant myeloma cell lines lacking or expressing multidrug resistant protein ABCB1.

B) Cytotoxicity of anti-myeloma drugs in ABCB1+ and ABCB1- carfilzomib-resistant cells. Pomalidomide and iberdomide failed to induce cytotoxic effects in both carfilzomib-resistant sublines even at concentrations up to 500 µM. The other drugs produced meaningful IC50 values.

C) MMDR score for tested drugs, given as a ratio between IC50 in ABCB1+ and ABCB1- carfilzomib-resistant myeloma sublines, indicates if ABCB1 confers considerable resistance to the drug. Low (<2.0) MMDR score (black bars); Moderate (>2.5 and <5.0) MMDR score (pink bars); High (>5.0) MMDR scrore (red bars)

A



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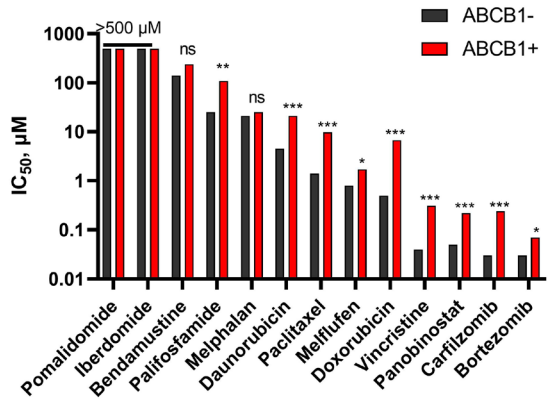

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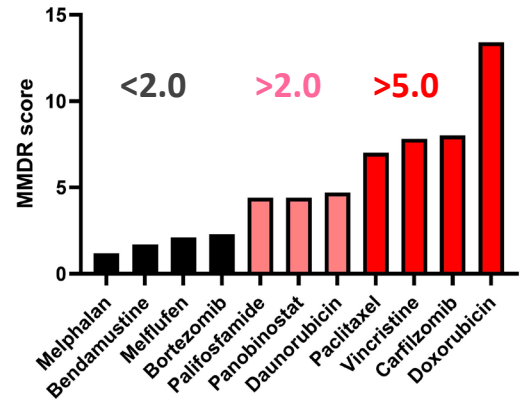


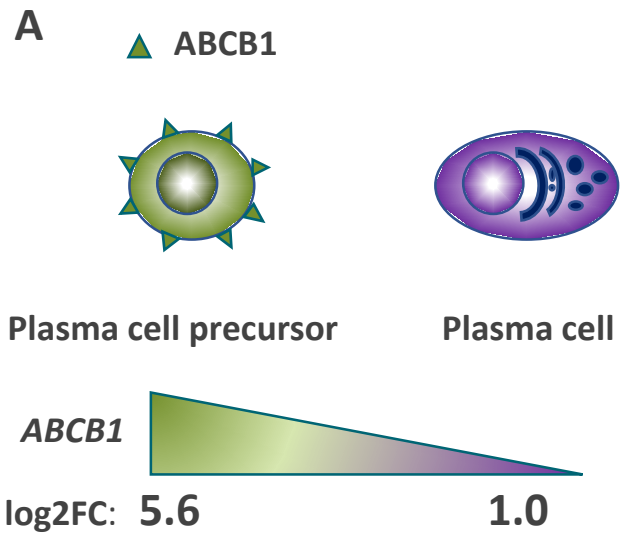
$$MMDR = \frac{IC_{50}\ (ABCB1^{+})}{IC_{50}\ (ABCB1^{-})}$$

Differential effect of ABCB1 on anti-myeloma drugs in carfilzomib-resistant myeloma model

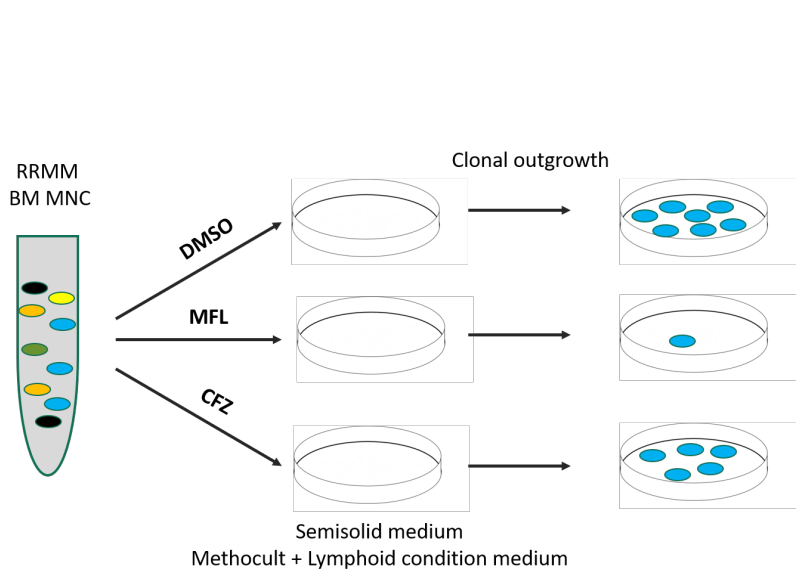
A) *ABCB1* mRNA is up-regulated in plasma cell precursors ($log_2FC = 5.65 \pm 0.32$, U test $p < 0.001$), in comparison to plasma cells.

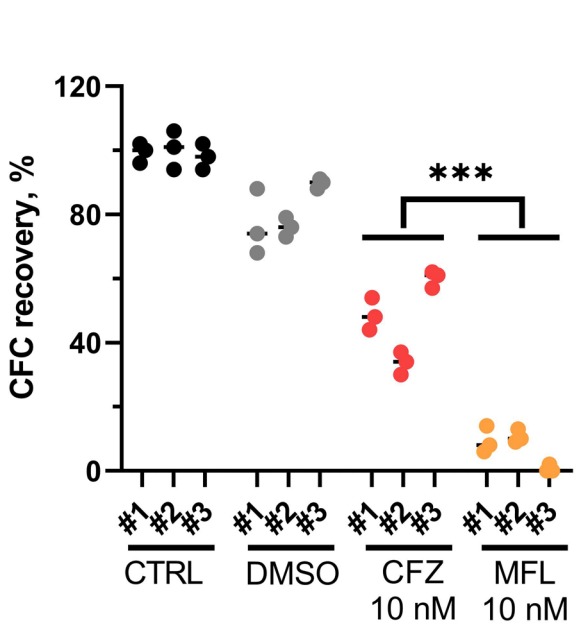
B) Experimental set up of colony-forming cell (CFC) recovery from RRMM BM MNC, indicative of the drug effect on myeloma precursors.

C) RRMM CFC recovery from BM MNC upon treatment with DMSO, 10 nM carfilzomib (CFZ), and 10 nM melflufen (MFL). ***, p<0.001, U test.



Source: GSE13411





Conclusions

- High *ABCB1* expression is still accosicated with poor response in era of novel anti-myeloma drugs.
- *ABCB1* murine homologue *Abcb1* is up-regualted in EMD-prone murine MYC-driven MM model.
- Increased ABCB1 activity in carfilzomib-resistant multiple myeloma (CFZ-RMM) has a differential effect on anti-myeloma drugs.
- Pomalidomide and iberdomide show no cytotoxic effect in CFZ-RMM cells.
- Melflufen, melphalan, bendamsutine, and bortezomib are only slightly affected by ABCB1 expression and activity in CFZ-RMM cells.
- Panobinostat, daunorubicin, paclitaxel, vincristine, doxorubicin, carfilzomib are strongly affected by ABCB1 expression and activity in MM cells.
- *ABCB1* mRNA is up-regulated in plasma cell precursors.
- Melflufen (low MMDR score), but not carfilzomib (high MMDR score), prevents myeloma clonal outgrowth from RRMM bone marrow MNC.