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Improving the activity of proteasome inhibitors for potential treatment of

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Traditional chemotherapy fails to cure renal cell carcinoma (RCC), hence novel approaches and mechanisms need to be exploited.Proteotoxic stress-induced apoptosis can be induced in cancer cells by interfering with the homeostasis of protein biosynthesis and destruction at various levels1,2: These include interfering with cellular substrate and oxygen supply, activation status, proteasomal and nonproteasomal proteolytic capacity and activity of the unfolded protein response (UPR). RCC has been shown to be sensitive for proteotoxic stress induced apoptosis and the proteasome plays a pivotal role in the pathogenesis of RCC so that proteasome activity in serum represents an unfavorable prognostic marker in RCC3. Proteasome inhibition with the first-generation drug, bortezomib, has shown a durable antitumor effect only in a minority of patients with advanced RCC and was hampered by drug-induced side effects. Today, a decade later, the knowledge about the role of the proteasome and mechanisms of proteasome inhibitor resistance has significantly improved, as did the ability to synthesize subunitselective, proteasome specific and hence more effective next generation proteasome inhibitors. Also the development of improved methods to analyze proteasome activity and biology in primary tissues
opened new potential options. We here aim to re-visit the issue of identifying potential treatment Options of RCC with proteasome inhibitors, applying the actual knowledge from the multiple myeloma (MM) field in conjunction with most recent proteasome inhibition and analysis technology to the field of RCC.

The aims of the current research project are to explore the potential to improve activity of proteasome inhibition against RCC by three strategies:
• increasing the sensitivity of RCC cells for proteasome inhibition via modulation of the activity of the unfolded protein response
• increasing the degree, duration and selectivity of proteasome inhibition by using nextgeneration, irreversible proteasome inhibitors with improved selectivity and high activity, in particular against the β5 and β2 subunits of the proteasome
• exploring the role of the immunoproteasome in primary RCC samples and potential selective immunoproteasome inhibition as therapeutic strategy against RCC

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keywords	-
project homepage	-
project partner	-
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end of project	2018
additional information	-
project manager	Dr. Dominik Abt