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Title: Mesoporous silica-based nanoparticles for targeted delivery of proteasome inhibitors to the lung

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Body: The ubiquitin-proteasome system (UPS) is responsible for the degradation of over 90% of all cellular protein and therefore plays an essential role in a plethora of cellular processes. Due to the important role of the UPS in cell cycle regulation, inhibitors of the proteasome represent promising antitumor agents. However, the application of high doses of proteasome inhibitors is restricted due to adverse systemic side effects. Local and targeted delivery of proteasome inhibitors into the lung may overcome these side effects. The aim of the project is to provide proof-of concept evidence for the application of proteasome inhibitors encapsulated in mesoporous silica-based nanoparticles (MSN's) as a valid therapeutic avenue for lung cancer. The MSN particles were functionalised with bioresponsive caps to allow a targeted release of inhibitors in environments with high local concentrations of MMP9 as found in tumor regions. After successful synthesis and characterisation of the particles, the efficacy of controlled drug release from the particles was proven in an in vitro approach using fluorescence release studies in the presence of recombinant MMP9. Next, we assessed particle toxicity and specific drugrelease in lung cancer cell lines transfected with MMP9 cDNA. We show that these novel particles can specifically release proteasome inhibitors at high MMP 9 concentrations as evidenced by activity profiling of the proteasome without showing particle toxicity. The use of nanoparticles for local drug delivery of proteasome inhibitors for cancer therapy has hitherto been unexplored and is expected to allow for higher local doses of proteasome inhibitors that more effectively kill tumor cells.