# Chaperons-inspired peptide nanofibers interrupt Cu (I) homeostasis in cancer cells.

M.T Jeena, David Ng, Tanja Weil

Max Planck Institute for polymer Research, Ackermannweg 10, 55128 Mainz

Supramolecular assembly of peptides within the cancer cell has emerged as a promising strategy for inducing cancer cell death. In this innovative approach, soluble amphiphilic peptide self-assembles into well-defined nanostructures inside the cancer cell in response to specific stimuli, under the condition of molecular crowding or due to the localization inside the confined space such as mitochondria.[1] Initially non-functional in their soluble state, these peptides become activated within the cell upon forming supramolecular structures, typically nanofibers. Previous studies have illustrated the ability of intramitochondrial formed nanofibers to interact with the mitochondrial membrane, ultimately initiating apoptosis. In here, we demonstrate the capability of *in cellulo* formed peptide fibers to disturb the copper (I) ($Cu^+$) homeostasis of cancer cells to induce cell death, which could not be achieved by the small molecules.

$Cu^+$ homeostasis is upregulated in many cancers and contributes to tumorigenesis. However, interrupting $Cu^+$ homeostasis inside the cell by small molecule is challenging because of their poor binding affinity compared to the intracellular ligands that bind $Cu^+$ with extremely high binding affinity. This challenge was successfully addressed by designing a $Cu^+$ chaperon derived peptide sequence Nap-FFMTCGGCR that assembles into nanofibers inside the cell under the condition of molecular crowding. Nap-FFMTCGGCR fibers demonstrated high affinity towards the $Cu^+$ which was comparable to the intracellular $Cu^+$ binding chaperons or ligands. Nap-FFMTCGGCR fibers induce over production of ROS, reduced the activity of Super oxide dismutase 1 (SOD 1), and ultimately induced the cellular apoptosis of triple negative breast cancer (MDA-MB-231) cells. In contrast, Nap-FFMTCGGCR has minimal impact on normal HEK 293T cells. Control peptides show that the self-assembly and $Cu^+$ binding properties must work in synergy to successfully disrupt $Cu^+$ homeostasis. We show the assembly-enhanced affinity for metal ions opens new therapeutic strategies to address disease-relevant metal ion homeostasis.[2]

References

1. Jeena, M. T. *et al.* Mitochondria localization induced self-assembly of peptide amphiphiles for cellular dysfunction. *Nat Commun* **8**, (2017).

2. Jeena, M. T. et al. Chaperone-derived Cu (I)-binding peptide nanofibers disrupt copper homeostasis in cancer cells. doi:10.26434/chemrxiv-2024-v04mz.