Review of: "DNA-based platform for efficient and precisely targeted bioorthogonal catalysis in living systems"

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This is an excellent article from a multidisciplinary team, which demonstrates beyond reasonable doubt the ability of DNA-templated copper nanoparticles to perform **CuAAC *in vivo*.** Moreover, the researchers achieve **targeting** by appending cell-specific aptamers to their 'click chemistry' catalysts and showcase the efficacy of the hybrid platform in *C. elegans* and mouse models by selectively activating fluorescent and drug-like triazoles.

The paper and the extensive supporting information provide numerous control studies and toxicity data, which show that neither the individual azide and alkyne prodrugs, nor their most active Apt-Cu^{30} complex cause significant cell death on their own for a prolonged period of several days. This is particularly important to assuage the critics of Cu-mediated bio-orthogonal reactions, such as Prof. Carolyn Bertozzi, who maintain that copper is universally cytotoxic. It appears that the neutral metal nanoparticles surrounded by negatively-charged DNA are perfectly tolerated by a wide variety of cells and even living organisms at the low micromolar concentrations necessary for CuAAC.

While the mechanism the azide-alkyne cycloaddition by Aptamer-CuNP in cytosolic conditions warrants further investigation, the *in vitro* fluorescent kinetics studies and the ICP-MS analysis of cancer cell lines offer ample evidence to the generality of the process. It will be exciting to see other researchers reproducing these findings in different contexts and thus greatly expanding the scope of CuAAC in living systems.