Modern trends in targeted structure-based drug design and discovery

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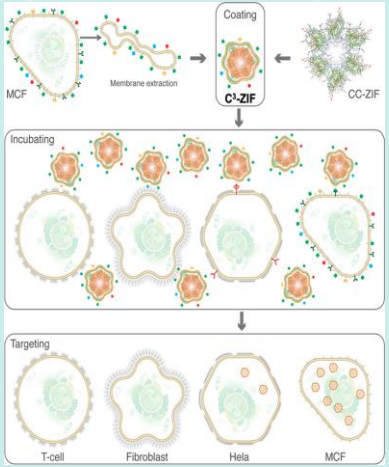
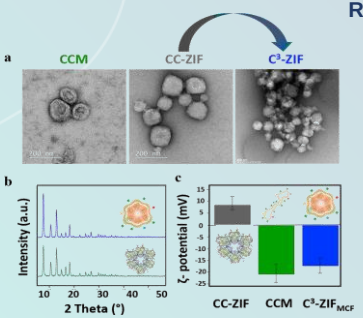
Cell-Type-Specific CRISPR/Cas9 Delivery by Biomimetic Metal Organic Frameworks

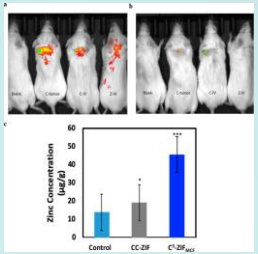
Abstract: Effective and cell-type-specific delivery of CRISPR/Cas9 elements is a problem. We developed biomimetic cancer cell coated zeolitic imidazolate frameworks (ZIFs) to provide genome editing machinery. Coating CRISPR/Cas9-encapsulating ZIF-8 with a cancer cell membrane created C^3-ZIF. MCF-7 cells had the maximum absorption of C^3-ZIF_{MCF} compared to other cells. When MCF-7 were transfected with C^3-ZIF_{MCF}, EGFP expression was repressed 3-fold, compared to 1-fold when transfected with C^3-ZIF_{HELA}. In vivo studies validated the selectivity for C^3-ZIF_{MCF} to accumulate in MCF-7 tumor. This validates the biomimetic approach's potential to fit the demands of cell-specific targeting, the most essential stage in the future translation of genome editing technologies.

Schematic Illustration of the Preparation and Cell-Type Selectivity of C^3-ZIF



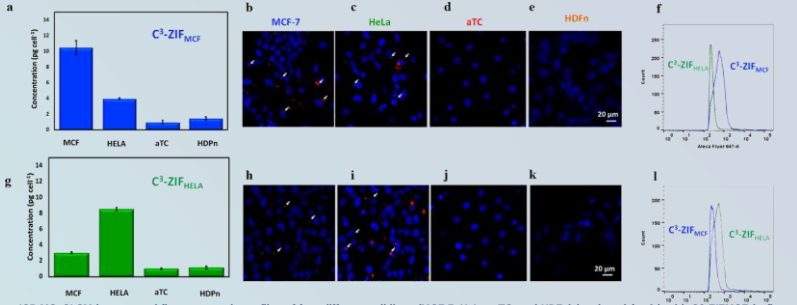


Characterization of C3-ZIF. (a)TEM (b) PXRD (c) ζ-Potential

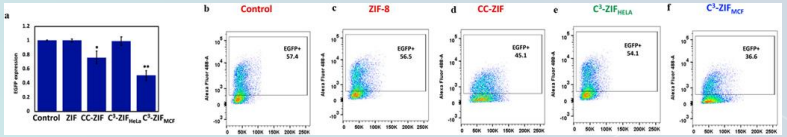


In vivo fluorescence imaging of MCF-7 breast cancer tumor-bearing mice

Results and discussion



ICP-MS, CLSM images, and flow cytometric profiles of four different cell lines (MCF-7, HeLa, aTC, and HDFn) incubated for 6 h with C3-ZIFMCF (a–f) and C3-ZIFHELA (g–l)



Genome editing by ZIF-8, CC-ZIF, C^3-ZIF_{MCF}, and C^3-ZIF_{HELA}. Quantitation of EGFP expression by qPCR and flow cytometric.

Conclusion: Biomimetic cancer cell membrane coating allows for a unique cancer targeting strategy due to the inherent homotypic binding phenomenon frequently observed among tumor cells. Coating CC-ZIF with CCM aided in mimicking the antigenic diversity of a cancer cell and incorporating unique surface functionalities that are hard to achieve using conventional synthetic methods. For genome editing, a 3-fold repression in the EGFP expression when MCF-7 were transfected with C^3-ZIF_{MCF} was observed, and the EGFP fluorescence was also decreased by 24% compared to 1-fold repression in the EGFP expression and 3% decrease of the EGFP fluorescence when MCF-7 were transfected with C^3-ZIF_{HELA}. In vivo results further verified our findings, as C^3-ZIF_{MCF} showed a targeted accumulation in MCF-7 tumor mouse models. The fabrication of ZIF-8 enriched with cancer antigenic materials allows for the replication of specific biological functions and enhances the accumulation within the source cells, which critically improves the targetability of any gene editing machinery.

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