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Nanocarrier-based Mitochondria-targeted Drug Delivery Systems

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Sub-cellular drug delivery is emerging as the new frontier in drug delivery. It has become more and more evident that the efficiency and efficacy of drug action depends largely on how well an unaided drug molecule is able to reach its intracellular target or even its target inside organelles such as mitochondria. Subsequently, the specific delivery of a drug to its site of action inside cells will dramatically improve its action. A random observation at the laboratory bench has helped pave the way towards the development of organelle-targeted pharmaceutical nanocarriers. A fortuitous discovery in the mid-1990s involving the self-assembly of a molecule, known to accumulate inside mitochondria, has led to the development of subcellular nanocarriers suited for the selective delivery of biological active molecules to mitochondria inside living mammalian cells. Mitochondria play a key role in apoptosis and several clinically used as well as experimental drugs are known to trigger apoptosis by directly interacting with target site at or inside mitochondria. Therefore we hypothesized that that the mitochondria-targeted delivery of such drugs will dramatically increase their pro-apoptotic activity. We have been developing during the last years a variety of mitochondria-specific pharmaceutical nanocarriers for the purpose of delivering therapeutic DNA or low-molecular weight compounds to mitochondria inside living mammalian cells. Here we will summarize our efforts and introduce new data demonstrating the applicability of our mitochondria-targeted nanocarriers for the delivery of biologically active molecules to mitochondria in living mammalian cells *in vitro* and *in vivo*.

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Cyclodextrin-based Porous Solids as Excipients for Improved Bioavailability of Drugs

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Cyclodextrins are cyclic structures composed of D- glucopyranosyl residues linked by α-1,4 glycosidic bonds to form a ring with a hydrophobic interior and a hydrophilic exterior. This structure gives cyclodextrins the capability to host hydrophobic guest molecules inside the ring. The CD traps the guest and becomes a guest-CD complex that makes the normally hydrophobic guest water-soluble due to the CD's hydrophilic exterior. Given this capability, cyclodextrins have been used in the pharmaceutical industry as drug excipients. Unfortunately, the utilization of CDs in pharmaceuticals is limited due to the low drug-loading efficiency. CDs come in amorphous powders, and it is difficult to uniformly mix hydrophobic drug compounds and CDs with sufficient solubility such that the drugs are driven to enter into the CD cavities. However, a new class of porous crystalline solids comprised of cyclodextrin molecules called Cyclodextrin Metal-Organic Framework ("CD-MOF") provides a solution. Porous CD-MOF can absorb and soak up drugs at high storage capacity to create a stable drug dosage form that readily forms drug-CD complexes upon dissolution of the CD-MOF exterior walls in water. Some of the major challenges in drug development involve the bioavailability of the drug compound, its stability, and the dosage of the compound over time. CD-MOFs can form the soluble drug-CD complexes, make the drug stable with encapsulation in the CD- MOF shell, and possess controlled dosage release. Over time, the CD-MOF exterior will dissolve in water and cause the outer cyclodextrins to detach from the framework and at the same time, form water-soluble drug-CD complexes.

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