Title:	Small Molecule Derived Nanotheranostics for Alzheimer's Disease
Authors:	Manju, Sharma
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Abstract: Brain, being the center of control for the body, is capable of causing major threat to life in case of any malfunctioning. Other than cardiovascular and pulmonary disorders/diseases, steep rise in global burden of neuronal disorders especially Alzheimer's disease (AD) is one of the major public health concern in today's world. The aggregation and accumulation of neurotoxic amyloid-β (Aβ) and hyper-phosphorylated tau proteins are the major neuropathological hallmarks of Alzheimer's disease (AD). Inhibiting their aggregation is one of the most viable approaches for controlling the progression of this deadly disease. Currently available anti-AD drugs have many limitations such as their limited ability to pass through the blood−brain barrier (BBB), low bioavailability in the central nervous system (CNS). Their several physicochemical characteristics like low lipophilicity, high molecular weight (MW), and higher polar surface area, also hinder their successful brain delivery. Therefore, it becomes imperative to look for more efficient and disease modifying anti-AD drugs. New generation theranostic nanomedicines can serve as cutting-edge and safer solutions to overcome these existing limitations and improve current treatment stratagems for the disease with potential clinical success. In this regard, the present thesis is focused on the development of small molecule derived nanotheranostics for imaging and potential therapy of Alzheimer's disease. In the very first study, we developed self-fluorescent solo tryptophan nanoparticles (TNPs) from a single amino acid, L-tryptophan by a simple hydrothermal reaction. We demonstrated that TNPs could significantly inhibit as well as disrupt the fibrils formed by Aβ42 peptide, and a reductionist approach based amyloid model dipeptide, phenylalanine-phenylalanine (FF). More importantly, these nanoparticles were non-toxic to neuronal cells and could protect the neurons from Aβ42 peptide and FF aggregates induced cytotoxicity. In addition, efficacy 20studies performed in animal models further revealed that the TNPs could rescue spatial and learning memory in intracerebroventricular (ICV) STZ administration induced AD phenotype in rats. Moreover, pharmacokinetics studies further established the BBB permeability and brain delivery potency of TNPs. Inherent excellent fluorescent properties of these nanoparticles could further be exploited to use them as imaging modalities for tagging and detecting FF and Aβ42 peptide fibrils. Thus, the biocompatible and utterly simple and fluorescent tryptophan nanoparticles synthesized here could serve as potent nanotheranostic agents for treating and diagnosing AD. Stepping forward, we next tried to explore the anti-amyloid propensity of theranostic tryptophan nanocomposite with another anti-amyloidogenic and neuroactive molecule, dopamine. The nanocomposite (DTNPs) was developed by following a simple hydrothermal reaction. Interestingly, the designed multimodal theranostic system carried triple advantages: (a) amyloid recognition and binding capacity owing to the presence of the aromatic moiety specifically tryptophan, (b) Aβ-polypeptide fibril disaggregation propensity contributed by the presence of both tryptophan and dopamine, and (c) inherent BBB permeability by means of tryptophan. Further, the DTNPs showed synergistic neuroprotective effects against both in neuroblastoma cells and in animal model (ICV-STZ) of dementia. In addition, DTNPs exhibited excellent fluorescent properties and light up the cytoplasm of neuroblastoma cells when being incubated with cells, confirming their ability to serve as an intracellular bioimaging agent. Thus, our overall results of this study signify the potency of the DTNPs as promising multifunctional theranostic agents for treating AD. Despite the promising anti-amyloid potency of both solo tryptophan and nanocomposite of tryptophan toward both FF-derived amyloid fibrils and preformed Aβ-peptide fibers, the anti- aggregation property of nanosystems against tau protein were not explored. Thus, in our next study we have tried to develop a dual functional fluorescent resveratrol and L-tryptophan 21(Res- Trp) loaded dopamine (dopa) core nanotheranostic system as a dual anti-amyloid agent. The nanosystem demonstrated dual anti-amyloidogenic activity against both Aβ42 peptide, and the hexapeptide Ac-PHF6 (VQIVYK) derived from tau protein. Additionally, Res-Trp loaded Dopa core showed remarkable neuroprotective effect in neuroblastoma cells against both FF amyloid fibrils and hexapeptide Ac-PHF6 fibrils induced toxicity under the NIR laser irradiation. Our dual functional nanosystems thus serve as new class of theranostic systems for combating the AD. In addition to simple small molecule based nanotheranostic systems for treating and diagnosing AD, we tried to explore dopamine coated piezoelectric polyvinylidene fluoride (DPVDF) nanospheres as acoustic stimulus (sonication) triggered anti-fibrillizing agents towards FF, as well as Aβ42-polypeptide fibrils. DPVDF nanospheres represent a class of biocompatible piezoelectric materials with piezo-catalytic property triggered in response to acoustic stimulus. The acoustic stimulus-activated DPVDF nanospheres produced piezo- induced oxidative stress, under both in vitro and in cellular conditions, which successfully destabilized FF and Aβ42 fibrils. In vitro studies also revealed that the stimulus-activated DPVDF nanospheres could efficiently alleviate the neuro-toxicity of FF fibrils as exemplified in the neuroblastoma, SHSY5Y cells. Thus, these acoustic stimuli activated nanospheres could serve as novel class of disease modifying nanomaterials for non-invasive electro- chemotherapy of AD. Overall, this thesis demonstrates the development of different small molecule derived nanotheranostic systems, capable of transversing the BBB to serve as simultaneous amyloid inhibitors and aggregate detecting agents under one roof. Such multifunctional nanosystem are not only interesting but also superior to many other reported anti-amyloid nanostructures in terms of their biocompatibility and ease of fabrication.

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