biological studies of genetic transformation in cells and cell networks to industrial applications of high throughput cell based genetic assays.

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P16

Peptide nanofiber scaffold for brain repair and axon regeneration with functional return of vision. Where do we go from?

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Nanotechnology is often associated with materials fabrication, microelectronics, and microfluidics. Until now, the use of nanotechnology and molecular self assembly in biomedicine has not yet been explored to repair injured brain structures. In order to achieve axonal regeneration after injury in the central nervous system several formidable barriers must be overcome, such as scar tissue formation after tissue injury; gaps in nervous tissue formed during phagocytosis of dying cells after injury and the failure of many adult neurons to initiate axonal extension. Using the mammalian visual system as a model, we report that a designed self-assembling peptide nanofiber scaffold creates a permissive environment not only for axons to regenerate through the site of an acute injury, but also to knit the brain tissue together in both young and adult animals. In experiments using a severed optic tract in the hamster, we show that regenerated axons reconnect to target tissues with sufficient density to promote functional return of vision, as evidenced by visually elicited orienting behavior in adult hamsters. The peptide nanofiber scaffold not only represents a new nanobiomedical technology for tissue repair and restoration, but also raises the possibility of effective treatment of central nervous system and other tissue or organ trauma.

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P17

Effect of oxidative stress on α-synuclein aggregation in Parkinson's disease

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Parkinson's disease (PD) results from a progressive loss of dopaminergic neurons from the substantia nigra in the midbrain. The postmortem brains of Parkinson's patients are characterized by mitochondrial complex I impairment, oxidative damage, and the presence of cytosolic inclusions named Lewy bodies. Lewy bodies are enriched with aggregated, oxidatively modified forms of the presynaptic protein α-synuclein. Complex I inhibitors such as rotenone and MPTP elicit oxidative stress and induce the aggregation of α-synuclein in cellular and animal models of PD. To investigate the link between complex I impairment and sequence-specific, post-translational modifications of α-synuclein, the protein was isolated from rotenone-treated PC12 cells and analyzed by tandem mass spectrometry. We found that rotenone induced various modifications in the C-terminal region of α-synuclein, including oxidation of methionine, nitration and amination of tyrosine, and phosphorylation of tyrosine and serine. These modifications correlated with an increase in the levels of membrane-bound, oligomeric α-synuclein detectable by fluorescence lifetime imaging microscopy and lipid flotation. In parallel, we found that α-synuclein aggregation and toxicity were suppressed by DJ-1, an antioxidant protein that is dysfunctional in some cases of familial PD. Our findings establish a link between mitochondrial impairment, oxidative stress, and post-translationally modified α-synuclein isoforms that may be involved in neurodegeneration. A current goal in nanomedicine is to determine how the conformational behavior of α-synuclein is influenced by sequence-specific modifications using single-molecule approaches. The results of these experiments will provide insight into the pathogenesis of PD and stimulate novel therapeutic strategies in the treatment of this disorder.

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Huntingtin oligomeric structures and their potential neurotoxic role in Huntington's disease

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Huntington's disease is a hereditary neurological disorder characterized by the accumulation of misfolded protein aggregates in human post-mortem brain tissue. These aggregates, or inclusion bodies, resemble amyloid-containing plaques observed in Alzheimer's and Parkinson's diseases, and contain fibrillar material comprised of N-terminal fragments of the huntingtin protein. Amyloidogenic protein aggregation is a complex process likely to involve the assembly of multiple intermediate structures prior to the formation of fibrillar aggregates. Such fibrillization intermediates have been observed both in vitro and in vivo with A-beta in Alzheimer's disease and in vitro with α-synuclein in Parkinson's disease and include both globular oligomeric assemblies as well as protofibrillar structures, however the occurrence of huntingtin oligomeric species is not yet resolved. While the molecular mechanisms remain unclear, there is compelling evidence that these intermediate species play a critical role in neurotoxicity. Using a recombinant huntingtin exon-1 N-terminal fragment expressed in bacteria and purified using affinity chromatography, we have established an in vitro model to study huntingtin aggregation. Initial aggregation experiments using a combination of biochemistry and morphological analysis suggested that huntingtin, like Amyloid-beta and α-synuclein, also forms oligomeric and protofibrillar species. More recent studies using high resolution AFM and TEM revealed the formation of disc-like structures in the early stages of aggregation that were 2.5–5 nm in diameter, followed by the assembly of protofibrils and fibrils with a similar diameter. Congo red was shown to inhibit the formation of elongated mature fibrils, but not the assembly of smaller protofibrils. Biochemical isolation of these oligomeric structures followed by injection into cultured cells may implicate putative huntingtin intermediates in cytotoxicity and could serve as a target for therapeutic intervention.

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Nanoparticle probes with surface enhanced raman spectroscopic tags (SERS Dots) for cellular cancer targeting

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We have developed biocompatible, photostable and multiplexing-compatible surface-enhanced Raman spectroscopic tagging material (SERS Dots) composed of silver nanoparticle-embedded silica spheres and organic Raman labels for cellular cancer targeting in living cells. SERS Dots produced linear Raman signatures at their different concentration, allowing