Aggregate-binding aptamers for Parkinson´s disease diagnostics

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Parkinson's disease (PD) affects over 10 million people worldwide. The aberrant aggregation of alpha-synuclein, a protein involved in synaptic transmission, is one of the early events in the pathogenesis of PD, and the one most closely linked to pathology. My project investigates alpha-synuclein aggregate-binding aptamers as potential biomarkers. Aptamers are small nucleic acid molecules that can specifically bind cellular targets. There are three goals of my project, which all should come together at the end. *(1) Developing aggregate-binding synthetic Xeno Nucleic Acid (XNA) aptamers using Systematic Evolution of Ligands by Exponential Enrichment (SELEX).* There is currently no aggregate-specific aptamer for alpha-synuclein. By using SELEX we are able to screen libraries of aptamers, and to select for those that bind the aggregates with high specificity. Moreover, XNAs are synthetic nucleic acid analogues with a backbone that is not recognized by the cellular quality control mechanisms, and are more stable as a result. (Previously published in: Taylor A.I. et al. (2018) Curr. protoc. chem. biol. 10, e44) *(2) Developing aptamer-based biosensors for facile detection of alpha-synuclein aggregates in patient biofluids.* We are developing a sensor based on strand-displacement. This mechanism involves competitive binding between two aptamers and the target aggregates. This approach will enable us to use an aptamer in a biosensor to detect the level of alpha-synuclein aggregates in PD patients' biofluids (Ye C. et al. (2023) Nat. Nanotechnol, 1-8). *(3) Multimerization of aptamers.* To increase the binding avidity, aptamers are multimerized to increase the sensitivity of the diagnostic sensors, allowing detection of the target earlier in disease progression. In conclusion, we are developing XNA aptamers for alpha-synuclein aggregates using SELEX, and then multimerizing them to increase their binding avidity so that they can be used in electrochemical sensors.