(Dis)connecting Aberrant Nuclear Condensates and Neurological Disorders

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Research in our laboratory focuses on furthering our understanding of nuclear compartmentalization. To this end, we are developing novel methodology to study the interplay of membrane dynamics, liquid-liquid phase separation and protein quality control. Our ultimate goal is to understand how defects in these processes are connected to human disease. Here, our focus has been DYT1 Dystonia, a highly debilitating movement disorder. We uncovered molecular and cellular defects leading to this severe and incurable movement disorder. Recently, we developed diagnostic biomarkers that report on aberrant nucleoporin condensates that build up in response to congenital mutations in the AAA+ ATPase TorsinA. With these in hand, we developed imaging-based high-throughput approaches to identify new cellular activities that control condensation processes via genome-wide genetic screening. In analogous screening approaches, we are presently in the process of identifying small molecules that counteract pathological phase transitions. Given the shared "molecular grammar" of pathological condensates in a variety of neurological disorders, obtained compounds may have broader utility towards pharmacological correction of neurological disorders tied to pathological phase transitions.