Fibrillar protein deposits composed of the microtubule associated protein tau are a pathological hallmark of >20 fatal neurodegenerative disorders including Alzheimer’s disease (AD). Recent evidence suggests that short tau fibrils can transfer between cells and then recruit soluble tau monomers onto their ends. In this process the monomer assumes the structure of the fibril. It is thought that distinct fibril conformers are propagated in different tauopathies, contributing to the phenotypic diversity of these diseases. The coexistence of six different tau isoforms in the human brain adds a layer of complexity, because varying isoform ratios can influence fibril conformation. Using selectively labeled tau molecules in conjunction with electron paramagnetic resonance and fluorescence spectroscopy; and a variety of biochemical assays, we have gained insights into tau fibrillization. In this seminar I will discuss our current understanding of tau fibril structure, present molecular features that modulate seeding, and examine selective pressures that alter conformer populations in fibril ensembles. The recently published Cryo-EM-based molecular models of tau fibrils from AD brain will serve as an important reference point.