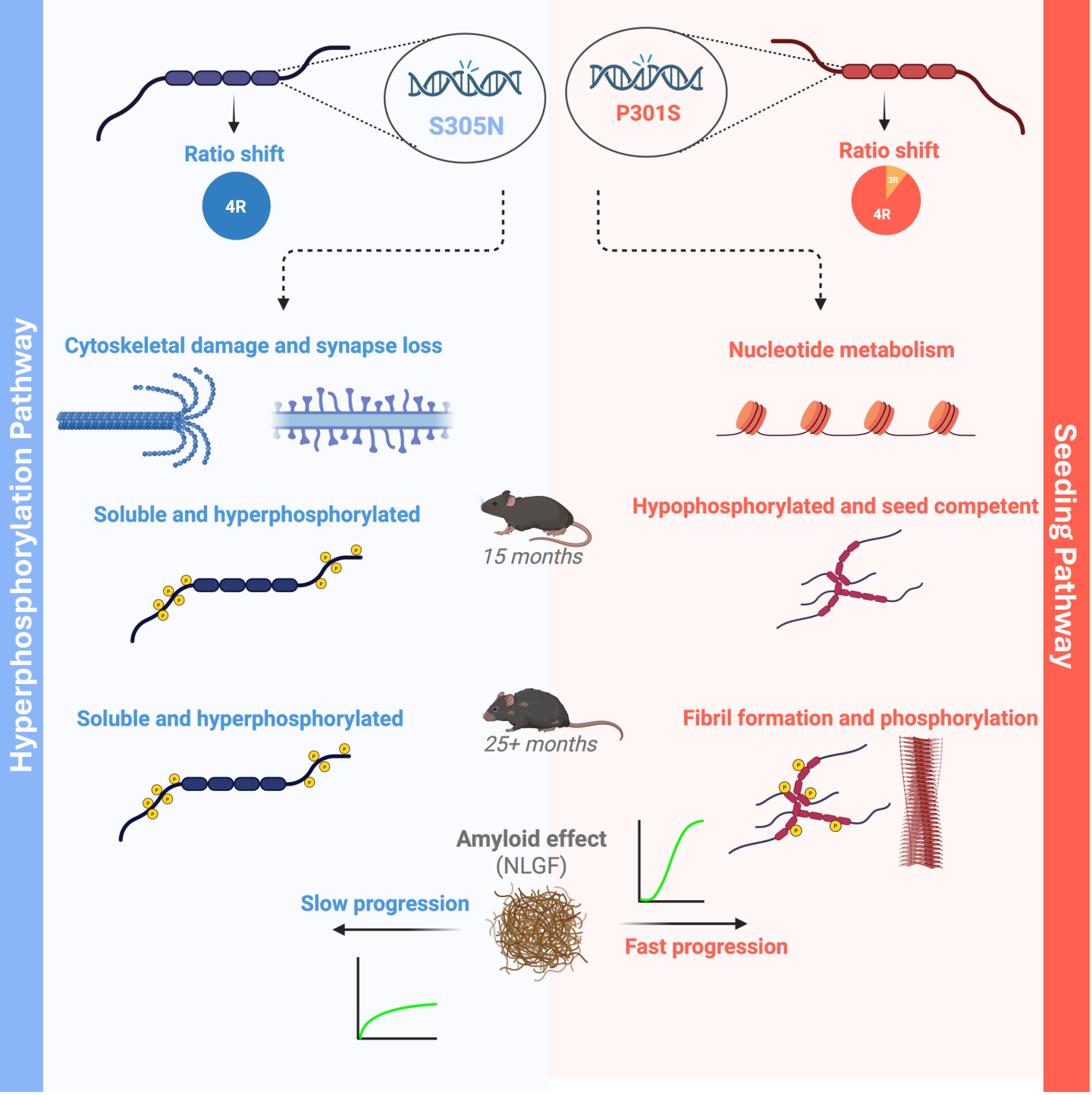

Graphical abstract. Schematic representation comparing two trajectories of tau pathology. The S305N mutation promotes a 4R isoform shift, cytoskeletal damage and synapse loss, and accumulation of soluble hyperphosphorylated tau. Tau remains soluble even at old ages. In contrast, the P301S mutation generates hypophosphorylated, seed-competent tau that forms fibrils. The effect of amyloid is slow in the S305N, but results in accelerated acceleration of pathology in the P301S. Figure made with Biorender.com.