The central theme of Kelly lab research at Scripps is to understand the kinetic competition between protein folding, misfolding, and aggregation—the latter two processes associated with neurodegeneration / organ deterioration. Kelly and Ron Wetzel were among the 1st to show that conformational changes were sufficient for protein aggregation (PMID 1390650). The Kelly lab paper on this subject also reported that transthyretin (TTR) tetramer dissociation is rate-limiting for TTR aggregation. They used this insight to conceive of TTR kinetic stabilizers, small molecules that bind to the native state selectively over the dissociative transition state to slow tetramer dissociation and prevent TTR aggregation from newly biosynthesized TTR (PMID 12560553). Because this strategy would not actively clear TTR amyloid already deposited, there was skepticism that this approach would be disease modifying. Kelly rationalized that the structurally heterogeneous TTR aggregates in circulation were also contributing to degeneration of post-mitotic tissue because they had access to far more biological processes than interstitial amyloid fibrils (PMID 33472954). The TTR kinetic stabilizer drug tafamidis (PMID 12820260) was the 1st drug to slow the progression of any human amyloid disease, demonstrating for the first time that pharmacological modification of protein aggregation could be disease modifying (PMID 8986762). These results emerged from a clinical trial largely conceived of by Teresea Coelho (PMID 22843282). The Kelly Lab also discovered that diflunisal, a Merch NSAID, could be repurposed as a TTR kinetic stabilizer (PMID 14711308). Yoshi Sekijima, then a post-doctoral fellow in the Kelly lab established the diflunisal dose effective for stabilization at Scripps (PMID 17107884), and John Berk and colleagues enabled a positive diflunisal clinical trial (PMID 24368466). Diflunisal is used effectively for hereditary TTR amyloid disease prevention and for treatment. Kelly also translated the T119M TTR genetic observation made by Teresa Coelho into a mechanistic biochemical understanding of amyloid disease prevention, i.e. they sorted out the interallelic trans suppression mechanism (PMID 11577236). Mat Mauer and Pfizer colleagues conceived of the tafamidis cardiomyopathy trial that resulted in a statistically significant reduction in the combination of all-cause mortality and frequency of cardiovascular-related hospitalizations leading to FDA (2019) and EMA (2020) approval of tafamidis (currently being administered to > 65,000 patients; PMID 30145929). In 2019 the Kelly lab in collaboration with Giampaolo Merlini reported results from an immunoglobulin light chain protease-coupled fluorescence polarization small molecule high throughput screen that produced the chemical matter that enabled full-length light co-crystallography, leading to the discovery of the immunoglobulin light chain small molecule kinetic stabilizer binding site (PMID 30971495). Protego Biopharma elaborated the clinical candidate from the precursor designed and synthesized by the Kelly lab into the kinetic stabilizer for treating light chain amyloidosis–Phase 1 Clinical Trial have been successfully completed, the IND submitted, and Phase 3 Clinical Trial are anticipated to start Q3 2026. The Kelly lab also Discovered the first example of functional amyloid fibrils in mammals (in melanosomes; PMID16300414). An author of > 425 papers (ISI Web of Science *h-index* = 110), Professor Kelly is a member of the National Academy of Sciences (USA), and the American Academy of Arts and Sciences (USA). Kelly has placed 47 trainees in academia and over 70 trainees in the biotechnology and pharmaceutical industries.