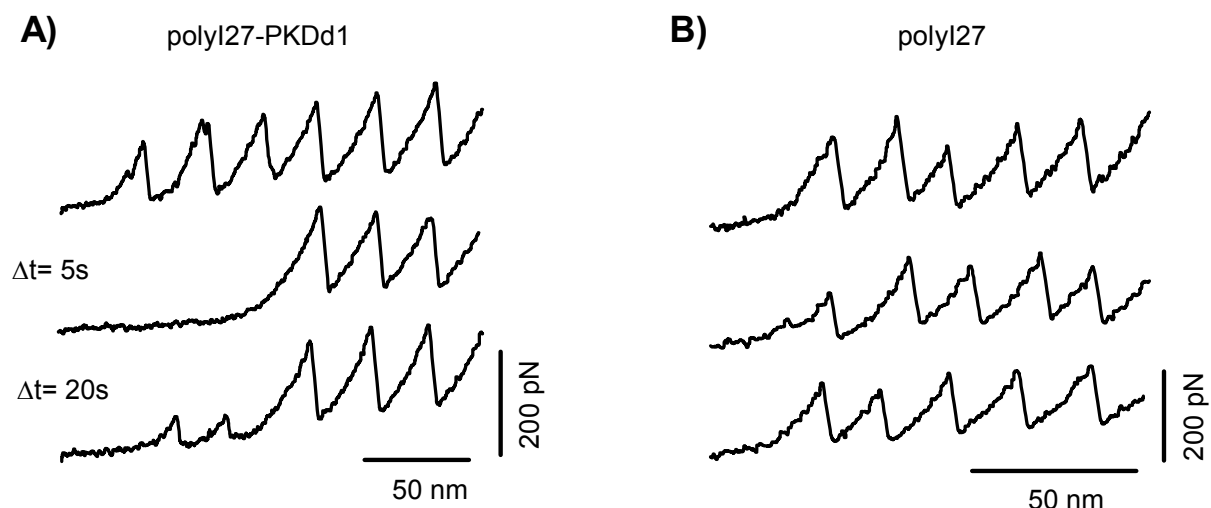**SUPPLEMENTARY MATERIAL**

Figure S1. Estimating the refolding rate of PKD domains. Measuring the refolding rate of PKD and I27 domains using a two-pulse stretching/relaxation protocol. Three consecutive force-extension are shown obtained with time delays of 5 s and 20 s for a HuPKD-I27 (A) and I27 polyprotein (B). In order to estimate the refolding rate of PKD domains we used a double-pulse unfolding/refolding protocol (Carrion-Vazquez et al., 1999; Oberhauser et al., 1998). A polyI27-PKDd1 molecule was first picked up and stretched close to its contour length and the total number of unfolded domains (N_{total}) was counted (six in this case) (Fig. S1A). Based on the molecular design of this heteropolyprotein, these six unfolding events should result from the unfolding of three PKDd1 and three I27 domains. Then the unfolded polypeptide chain was relaxed quickly to zero force before a second stretch. After a five-second relaxation, only three domains unfolded in the second pull indicating that three out of six domains refolded in five seconds (N_{ref}). These three refolded domains were interpreted as I27 domains based on the fact that they are known to refold within 5 seconds (Carrion-Vazquez et al., 1999; Fig. S1B). No refolded PKDd1 domains were detected during this time interval. We found that we had to wait as long as 20s to observe PKD refolding. Interestingly, the mechanical stability was much lower than in the control first pulse (~ 50 pN; Fig. S1A). This indicates that it took ~20 s for the PKD domains to collapse and form a folded domain but with a much lower mechanical stability. This inefficient and sluggish refolding of the PKD makes it not possible to study the effects of osmolytes on the refolding kinetics using AFM techniques.

A)

polyArPKD

B)

C)
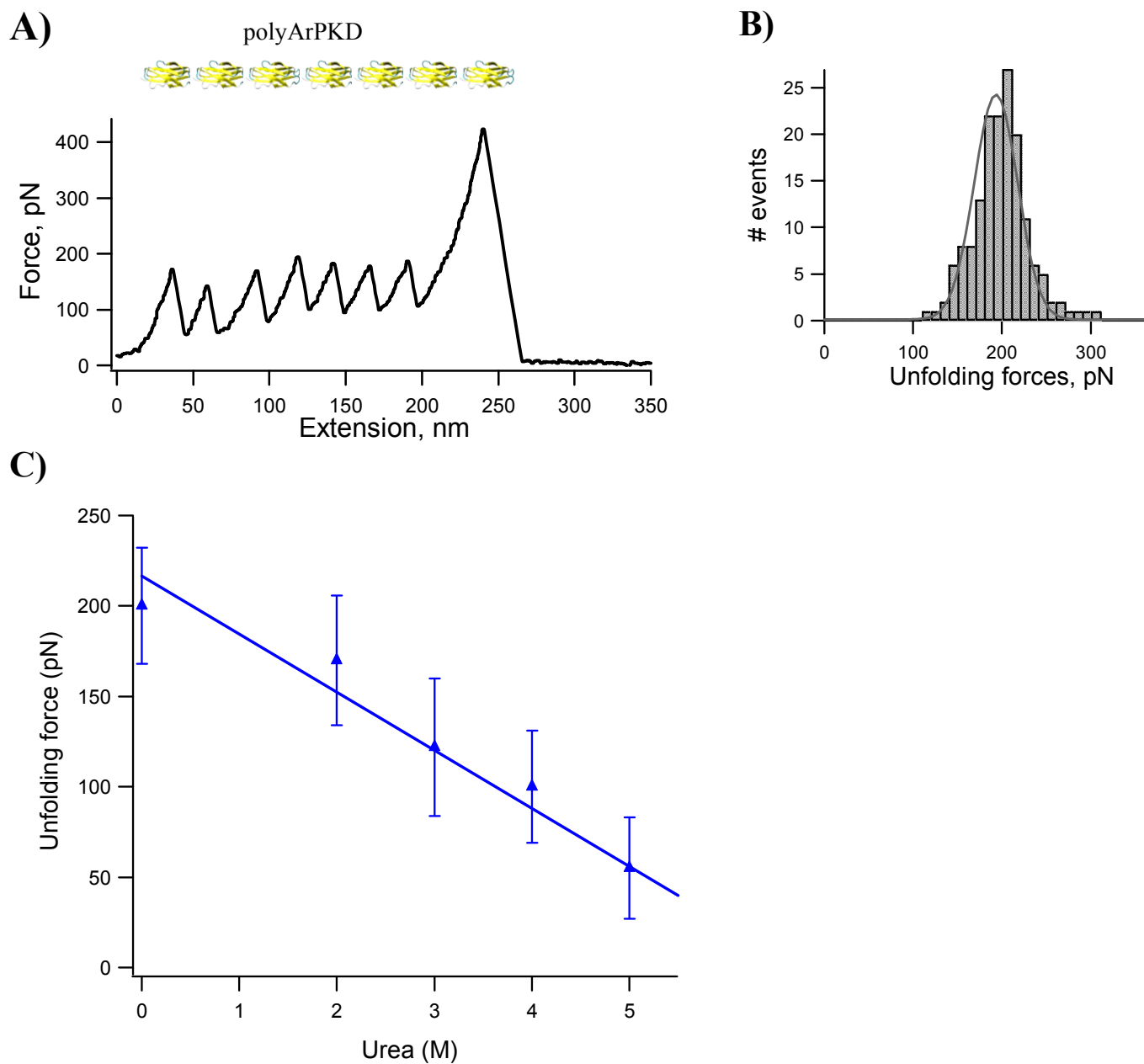
Figure S2. Effect of urea on the mechanical stability of an ArPKD domain. A) Typical force-extension obtained after stretching an ArPKD polyprotein. B) Unfolding force histogram shows that ArPKD domains unfold at about 200 pN (198 ± 31, n=160). C) Plot of the ArPKD unfolding forces as a function of the urea concentration. The line is a linar fit to the experimental data. The slope is 32 pN/M urea.