

## W0214

**Crystal Structures of Familial ALS SOD1 Mutant G85R.** Xiaohang Cao, Sai Seetharaman, Alexander B. Taylor, P. John Hart, Dept. of Biochemistry & the X-ray Crystallography Core Laboratory, Univ. of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229.

Mutations in copper, zinc superoxide dismutase (SOD1) are linked to adult-onset familial amyotrophic lateral sclerosis (FALS), a fatal neurodegenerative disorder. It has been proposed that the pathogenic SOD1 mutant G85R exerts its effects through a toxic gain of function, and has been reported to cause disease progression in transgenic mice despite its accumulation to low levels. One possibility is that G85R may have an increased propensity to engage in non-native SOD1-SOD1 interactions leading to aggregation. Here, we report the structures of G85R SOD1 in space groups  $I2_12_12_1$  and  $P2_12_12_1$  refined to 1.9 and 2.1 Å resolution, respectively. The overall structure is similar to wild type SOD1. However, in the  $P2_12_12_1$  structure one of the zinc sites remains unoccupied, leading to disorder in the zinc and electrostatic loops. This results in a similar packing to other metal-deficient pathogenic SOD1 proteins, H46R and S134N that form linear, filamentous arrays<sup>1</sup>. The fully metal-replete G85R protein in the  $I2_12_12_1$  system does not demonstrate this sort of interaction. The significance of these observations in the context of FALS is discussed.

<sup>1</sup>Elam, *et al.* (2003) *Nat. Struct. Biol.* 10: 461-467.