Based on depletion of rictor (an mTORC2-specific component), Lamming *et al.*[30] recently proposed that active mTORC1 represses longevity, while a functioning mTORC2 promotes longevity in males.

15.3 Rapamycin's Mysterious Effects on Aging

Over the years leading up to 2004, there were many approaches advertised to promote rejuvenation and longevity. Mainstream researchers were quite skeptical that a pill could be developed that would allay the deleterious effects of aging. A thought would go like this: aging is not a disease that can be treated. Given the safety profile of rapamycin at that time, it is remarkable that the Interventions Testing Program[32] (ITP) accepted the author's proposal in 2005 to test chronic treatment with rapamycin for longevity effects in mice. A key to these experiments proceeding was Randy Strong's development of encapsulation of rapamycin in Eudragit S100 (called eRapa), which accomplished two critical things; it stabilized the drug in food (around 80% is lost to degradation) and released rapamycin when the pH of the gut approached 7 (*i.e.*, the lower part of small intestine and colon), resulting in stable blood levels.[32] The ITP performed the first test of eRapa in an awaiting (and now older) cohort or UM-HET3 mice at each of test centers. Would it kill these old (60 in human years) mice? The results in 2009[33] were a major surprise: eRapa treatment beginning at 20 months of age resulted in extension of maximum life span in both males and females. The ITP has now repeated tests of eRapa in younger mice with the same results[34] and in the latest trial that showed dose- and sex-dependent effects on longevity.[35]

This is now very mysterious: the more that mice consume of this drug, previously thought to suppress immunity and increase risk of cancer, the longer they lived, especially females. It should be noted that eRapa chronically resulted in an extension of median and maximum life span, the latter result indicating that all causes of mortality were prevented, delayed or reduced in severity. Johnson *et al.* explored the limits of dosing by treating mice with nine times the original life extending dose of eRapa, and observed only a decrease in body weight (BW).[36]

15.4 Effects of Chronic Rapamycin on Age-Associated Diseases

These results prompted investigators around the world to test eRapa and other formulations on numerous age-associated diseases. The ITP and other groups investigated the question: does eRapa delay aging-associated traits? Wilkinson *et al.*[37] showed that eRapa beginning at 9 months of age "slows aging in (UM-HET3) mice," although noting a higher incidence of testicular degeneration and cataracts. Zhang *et al.*[38] investigated this question in an inbred strain, C57BL/6, starting the diet at 19 months of age and concluded that eRapa extended life and health span, with no differences noted in testicular degeneration or cataracts in older mice. This group followed up