

suppressor of osteosarcoma, in bone tumors.¹³⁴ Thus the effects of STACs in cancer appear to be tumor- and context-specific, and will need to be carefully evaluated in the future prior to their use in the clinic.

11.4.4 Neurodegenerative Disease

The pharmacokinetic properties of resveratrol allow it to cross the blood-brain barrier where it displays a broad range of neuroprotective effects.¹⁵ For example, intraventricular injection of resveratrol for one week was shown to improve learning and memory in aged mice, and to prevent cognitive decline.¹³⁵ These effects also appear to be conserved in nonhuman primates, as dietary supplementation with resveratrol was recently shown to confer neuroprotection in cortical brain tissue of monkeys fed a high-fat/high-sucrose diet.¹¹⁴ It also protects against the damaging effects of ischemia in the brain *via* a SIRT1-dependent mechanism.¹³⁶ In addition to these protective effects, resveratrol appears to be well suited for the treatment of a number of age-related brain disorders. First, resveratrol has been shown to prevent accumulation of beta-amyloid peptide¹³⁷ and to reduce plaque formation,¹³⁸ two processes that are involved in Alzheimer's disease. It also extends the lifespan of the senescence-accelerated mouse (SAMP), a model of Alzheimer's disease in which the amyloid precursor protein (APP) is over-expressed in the brain.¹³⁹ Second, resveratrol slows down the progression of Parkinson's disease.¹⁴⁰ Finally, two reports have shown that resveratrol improves motor neuron function and extends the shortened lifespan of the SOD1(G93A) mouse model of amyotrophic lateral sclerosis (ALS).^{141,142}

While several STACs, including SRT1720, SRT2104, and SRT3025, have been shown to penetrate into the brain, few studies have examined their efficacy for the treatment of age-related brain diseases.¹⁵ Nonetheless, one study demonstrated that SRT3025 protects against neurodegeneration and mimics the effects of CR on the brain.¹⁴³ Other studies have focused on using synthetic STACs to treat specific diseases not necessarily associated with age. For example, it was shown that SRT1720 is protective in a mouse model of multiple sclerosis,¹⁴⁴ and that SRT2104 can attenuate brain atrophy, improve motor function, and extend survival in the N171-82Q mouse model of Huntington's disease.¹⁴⁵ Given that synthetic STACs can cross the blood-brain barrier and appear to be well tolerated, further studies examining their neuroprotective properties and effects in Alzheimer's disease are warranted.

11.4.5 Cardiovascular Disease

Due to its many protective effects on the cardiovascular system,¹⁴⁶ ingestion of resveratrol has been proposed to account for the "French Paradox", the fact that certain European populations with high wine consumption have a low risk of heart disease despite consuming a fat-rich diet.¹⁰⁹ Resveratrol acts to prevent cardiovascular disease in at least four ways, not all of which are mediated through SIRT1.¹⁰⁹ First, resveratrol prevents the oxidation of