CHAPTER 15

mTOR, Aging and Cancer: Prospects for Pharmacological Interventions

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15.1 Rapamycin: A Brief History

This now familiar, but nevertheless remarkable, story begins at Ayerst Labs in Montreal, where scientists in the 1970s identified a lipophilic macrocyclic lactone antibiotic produced by *Streptomyces hygroscopicus* in a soil sample collected from Rapa Nui (Easter Island). Scientists dropped its development as a fungicide[1] upon learning that it inhibited the immune response in various cell culture and animal model settings (reviewed by Sehgal[2]). Assigned the generic name, sirolimus, Wyeth Ayerst marketed it as Rapamune to prevent host rejection of transplants, only later to discover rapamycin has anti-tumor activity. Pharmaceutical companies have developed a number of derivative compounds (rapalogs) with indications that include prevention of allograft rejection, anti-cancer and anti-restenosis.[3] Even at this early stage, the mystery was there but not mentioned—how could a drug that suppresses

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