CHAPTER 14

Extending Lifespan by Inhibiting the Mechanistic Target of Rapamycin (mTOR)

DUDLEY W. LAMMING[a,b]

[a]Department of Medicine, University of Wisconsin–Madison, Madison, Wisconsin, USA; [b]William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin, USA
*E-mail: dlamming@medicine.wisc.edu

14.1 The Discovery of Rapamycin and mTOR

Rapamycin is a polyketide produced by *Streptomyces hygroscopicus* and was originally identified as the active antifungal agent in a soil sample from Easter Island.[1] The ability of rapamycin to also inhibit the proliferation of mammalian cells led to its development in the 1990s as an immunosuppressant, and more recently to the FDA approval of rapamycin (sirolimus) and the rapamycin derivatives everolimus, temsirolimus, and zotarolimus for the treatment of specific cancers and in drug-eluting stents. The robust biological effects of rapamycin have spurred interest in understanding the molecular basis underlying its incredible potency. Rapid progress in the area was made in the 1990s following the identification of the immunophilin FK506-binding protein 12 (FKBP12) as a protein with extremely high, sub-nanomolar affinity for rapamycin.[2] Genetic screens in yeast concluded that the FKBP-rapamycin complex was the active agent as yeast mutants lacking the gene encoding

RSC Drug Discovery Series No. 57
Anti-aging Drugs: From Basic Research to Clinical Practice
Edited by Alexander M. Vaiserman

Published by the Royal Society of Chemistry, www.rsc.org