Supplementary Box 1. Key discoveries in research on the role of the mTOR pathway in epilepsy.

1964. Identification of rapamycin-producing Streptomyces hygroscopicus in soil samples from Rapa Nui (also known as Easter Island)[124]
1975. Purification of rapamycin[144]
1977. Identification of the immunosuppressive activity of rapamycin[93]
1984. Anti-cancer effect of rapamycin[43]
1991. Target of rapamycin, TOR1 and TOR2, discovered in yeast[58]
1993. Identification of germline TSC1 mutation in TSC[44]
1994. Mechanistic target of rapamycin, MTOR, identified in brain lysates of mammals[125]
1994. The first TSC animal model, the Eker rat with germline mutation in Tsc2[154,155]
1999. Rapamycin (clinically called sirolimus) approved by the US Food and Drug Administration (FDA) for use in preventing host-rejection in patients undergoing kidney transplantation
2001. The first epilepsy animal model, Pten KO mouse, by genetic activation of the mTOR pathway[6,78]
2002. The first TSC animal model with epilepsy, Tsc1 GFAP KO[141]
2008. Identification of the anti-epileptic effect of mTOR inhibitor in a TSC mouse model[158]
2009. Everolimus approved by US FDA as the first treatment for patients with advanced kidney cancer after failure of either sunitinib or sorafenib
2010. Clinical success of everolimus for treating epilepsy in TSC patients[74]
2010. Everolimus approved by the US FDA to treat subependymal giant cell astrocytoma (SEGA) associated with TSC
2012. Everolimus approved by the US FDA to treat patients with non-cancerous kidney tumor associated with TSC
2012. Identification of brain somatic mutations in PIK3CA-AKT3-MTOR pathway in HME[79,115]
2013. Prevention of epileptogenesis by sirolimus in PMSE with STRADA loss-of-function mutation
2015. Identification of brain somatic mutation in mTOR in FCD[83]
2018. Everolimus approved by US FDA for use to suppress partial-onset seizures in TSC
2018. Clinical trials on the use of everolimus in seizure associated with FCD underway