

Palomid 529 (P529), a Broad Spectrum Signal Transduction Inhibitor affecting the PI3K/Akt/mTOR Pathway Inhibits Spasms in a Rat Epilepsy Model Abstract

Paloma Pharmaceuticals, Inc. is an early stage drug development company focusing on pathologies showing an aberrant up-regulation of the PI3K/Akt/mTOR pathway including cancer, ocular diseases (macular degeneration and diabetic retinopathy), arthritis, fibrotic diseases (renal and pulmonary fibrosis), CNS (epilepsy and neurodegenerative diseases), antiviral (HIV/AIDS) and skin diseases (psoriasis, atopic dermatitis and photodamage/wrinkling). Paloma owns the intellectual property relating to a series of novel, proprietary, small molecule drugs created through an integrated design platform incorporating proprietary, customized and industry standard computational tools that has therapeutic potential for the treatment of the foregoing diseases. These small molecule drugs, "Palomids", have shown significant activity in the test tube and in animal models of disease. Epilepsy is a chronic neurologic seizure disorder characterized by repeated nervous seizures with interruption of normal brain activity. It is characterized by recurrent unprovoked seizures lasting from a few seconds to several minutes. Symptoms may include convulsions and loss of consciousness, blank staring, lip smacking or jerking movements of arms and legs. Epilepsy affects more than fifty million people worldwide and nearly three million people in the United States predicted to double by 2015. 30% of patients taking antiepileptic drugs continue to have seizures even while taking two or more antiepileptic drugs.

Tuberous sclerosis (TSC) is a syndrome attributable to mutations in either TSC1 or TSC2. Neurological manifestations are a predominant clinical feature and include early-onset epilepsy, mental retardation, developmental delay, and autism. Most neurological symptoms are thought to be attributable to the occurrence of cortical tubers which typically form at the gray-white matter junction. A cortical tuber is a region of the brain that develops abnormally through the formation of benign lesions that displace normal brain tissue. TSC is named after these growths. The TSC1 and TSC2 proteins form a relatively tight complex in cells which functions in the PI3K/Akt/mTOR signaling pathway (see P529 Signaling Pathway in Core Technology section of web site). Mutation of TSC1 or TSC2 causing TSC1 or TSC2 protein dysfunction leads to up-regulation of the PI3K/Akt/mTOR pathway. There are a variety of mouse models that have been developed to directly or indirectly affect TSC. These models include a murine model with loss of TSC1 in developing neurons, a kainate chemoconvulsant model which causes sustained neuronal depolarization, a PTEN murine model which encodes a suppressor of the PI3K/Akt/mTOR pathway causing its activation and a lipopolysaccharide (LPS)/doxorubicin (Dox) rat model of infantile spasm. The PI3K/Akt/mTOR pathway is activated in each of these models with TORC1 inhibitors, namely rapamycin, showing a reduction of the number of spasms over time. In the LPS/Dox infantile model we have found that P529, when compared to rapamycin, shows superior activity in reducing spasms.