Vysoce účinné a selektivní inhibitory kináz CK1 pro léčbu leukémie, lymfomů a solidních nádorů

Fáze vývoje technologie

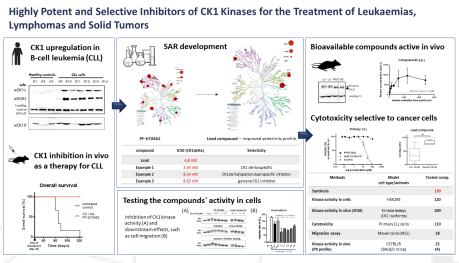
Preklinické testy

Status IP ochrany

Methodology patent PCT/CZ2013/000090 filled 5.8.2013, granted: CA, EP (CH, DE, FR, GB) Compounds patent EP18164938.5 application filed 29. 3. 2018

Strategie pro hledání partnera

Investice, Co-development, Licencování, Spin-off, Spolupráce



Instituce

MUNI CTT Centrum pro transfer technologií

Masarykova univerzita

Motivace

CLL is a lymphoproliferative malignancy with highly heterogeneous disease course and unclear pathogenesis, it is the most common adult leukaemia in western countries, however it is still considered as incurable, despite extensive effort invested in development of novel therapeutic strategies, albeit the new treatment options have significantly enhanced patients' response to therapy. Current therapy is directed at chemo-immunotherapy, with tyrosine kinase inhibitors targeting B cell receptor (BCR) signalling, although with a high percentage of failed/ relapsed cases, high toxicity and low percentage of complete remission. There is therefore a need for a complete cure – whether it is through novel targets and/or combination therapy.

Popis

The primary goal of the Masaryk University research group is to develop highly potent and selective inhibitors of casein kinase 1 (CK1), using the structure and binding mode of the known inhibitor PF-670462, with a main focus on CLL and lymphomas. The role of CK1 kinase in CLL pathogenesis has been demonstrated previously by this same research group. Other CK1-driven malignancies include solid tumors e.g. breast cancer, melanoma, prostate cancer, pancreatic cancer, ovarian cancer and hepatocellular carcinoma. The researchers have shown that the pharmacological inhibition of CK1interferes with development of B-cell leukemia in Eμ-TCL1 mice, and in the CLL in vivo proof of concept animal study, the CK1 inhibitor PF-670462 confirmed that combined treatment is superior to single-agent treatment by ibrutinib (the current state of the art CLL therapy). Selective inhibitors targeting CK1 kinases are currently NOT available for clinical use. Inhibition of CK1-driven signaling is a novel approach of leukemia and lymphoma treatment. Researchers at Masaryk University have synthesized >120 compounds and tested them for activity in vitro and in cells, with 25 compounds tested for activity in vivo in mice. Three

compounds have progressed to pharmacokinetic profiling. In vitro, results have indicated activity of compounds against primary targets, with sub-nM and single-digit nM IC50s, exceptional selectivity profiles and crystal structure in CK1 confirmed. In cells, efficacy has been demonstrated in stable cell lines and primary cells, and has been shown to have selective toxicity towards tumour cells. In vivo, compounds are orally bioavailable and welltolerated at therapeutic doses.

Komerční využití

Since the selective inhibitors targeting CK1 kinases are currently NOT available for clinical use our invention has a very attractive potential in treatment of numerous CK1- driven malignancies, ranging from cancer to neurodegenerative diseases or bipolar and sleeping disorders. The novel inhibitors of CK1 kinases have high activity against primary targets and an exceptional selectivity profile in vitro. They are orally bioavailable and well-tolerated at therapeutic doses in mouse model in vivo. Our technology is available for collaboration and/or licensing.