Pharmacological targeting of STK19 inhibits oncogenic NRAS-driven melanomagenesis

An international research team with multi-discipline expertise directed by Prof. Cui Rutao (major in biology) at the School of Medicine Boston University, Prof. Deng XianMing (邓贤明, major in medicinal chemistry) at the School of Life Sciences, Xiamen University, and Prof. Wang Peng (王鹏, major in clinical research) at Shanghai Cancer Center, Fudan University, recently reported a novel and viable therapeutic strategy for melanomas harboring NRAS mutations, which was published in *Cell* (2019, 176: 1113—1127. e16.). Both Prof. Deng and Wang received funding support from the National Natural Science Foundation of China for this work.

Oncogenic mutations of RAS family members are commonly found in 20%—30% of all human tumors. NRAS Q61 mutations are critical drivers of melanomagenesis which account for a quarter of melanoma. However, in contrast to the well-defined inhibitors targeting the oncogenic $BRAF^{V600E}$ mutation, no effective anti-NRAS therapies have been forthcoming. Here, a previously uncharacterized serine/threonine kinase STK19 was identified as a novel NRAS activator by the research team. STK19 phosphorylates NRAS at Serine 89 and activates oncogenic NRAS-driven melanomagenesis. A recurrent D89N substitution in STK19 found in 25% of human melanomas represents a gain-of-function mutation that interacts better with NRAS to enhance melanocyte transformation. $STK19^{D89N}$ knockin leads to skin hyperpigmentation and promotes $NRAS^{Q61R}$-driven melanomagenesis *in vivo*. Finally, they screened an in-house compound library and developed ZT-12-037-01 (1a) as a specific STK19-targeted inhibitor. ZT-12-037-01 (1a) effectively blocks oncogenic NRAS-driven melanocyte malignant transformation and melanoma growth *in vitro* and *in vivo*. Together, their findings demonstrate STK19 is an NRAS-activating kinase with frequent gain-of function mutations and provide evidence that pharmacological targeting of STK19 represents an effective therapeutic strategy for NRAS mutant melanomas.

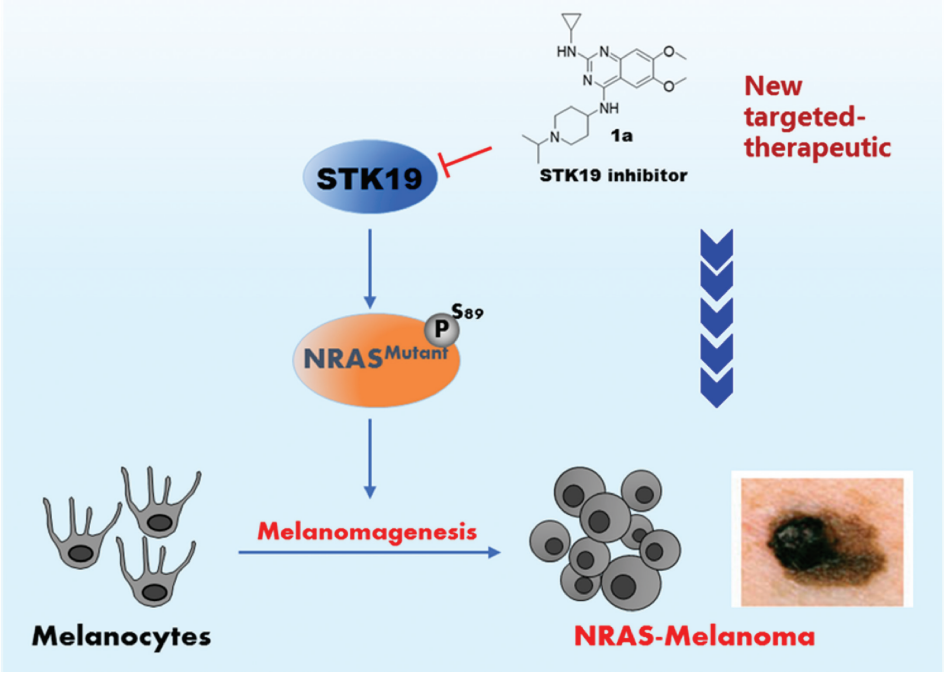

Figure Targeting STK19 blocks NRAS-driven melanomagenesis.