Development of anti-epileptic drug targeting KCNQ channels

KCNQ channels are proven anti-epileptic drug targets. We took advantage of two strategies to identify novel KCNQ activators. First, a library including 800,000 compounds was screened by traditional high throughput screening methods and a series of novel scaffolds were identified. Second, we performed a computer-aid virtual screening targeting the gating charge pathway of KCNQ2 channels. We provided evidence that the gating charge pathway of the voltage-gated KCNQ2 potassium channel can accommodate various small molecule ligands. The identified hits were then evaluated in various in vivo seizure models. System studies show that CF341 is an effective antiepileptic agent, with high activity, good metabolic characteristics, low toxicity (LD_{50}>1 g/kg) and other notable features when tested in vitro. Pharmacokinetic studies indicate CF341 and its major active metabolites have a high distribution rate in the brain, a long half-life and promising drugablity. CF341 is in preclinical trials and supported by the Key New Drug Creation and Manufacturing Program. Additionally, using the KCNQ activators as probes, we found the subtype selectivity of KCNQ channels is dynamically modulated by membrane lipids, which provide new insight into the action mechanism of KCNQ channels.

Zhaobing Gao
Professor, State Key Laboratory of Drug Research
Shanghai Institute of Materia Medica, Chinese Academy of Science