Screening and study of K^+ and Cl^- channel modulators

Ion channels are among the most commonly used drug targets. However selective and potent modulators of ion channels are still rare compared with identified numerous ion channels. Discovery and characterization of new modulators of ion channels are important in development of new efficient therapeutics for many diseases. Using an automated atomic absorption rubidium efflux assay (Aurora ICR 8000), we established a screening platform for modulators of K^+ channels and Cl^- channels. With Kv7/KCNQ K^+ channels as targets, we discovered a series of pyrazolo[1,5-a]pyrimidin-7(4H)-ones (PPOs) to be the activators of these family of K^+ channels. Based on structure-activity relationship (SAR), the substituted PPOs have been optimized, and a compound named QO-58 was identified as a novel, potent, and selective Kv7/KCNQ K^+ channel opener by patch-clamp assay. The QO-58 was further studied for its mechanism of action, for its antiepileptic effects, analgesic effects. QO-58 presents to be potentially beneficial in treating these diseases. We also established a screening system for the modulators of Ca^{2+}-activated Cl^- channels (CaCC)/TMEM16A using ICR 8000 assayed indirectly, by measuring excess silver ions (Ag^+) in the supernatant of AgCl precipitates. With this assay we have tested the effects of known Cl^- channel modulators on CaCC/TMEM16A, and also some new blockers of CaCC/TMEM16A were identified.

Hailin Zhang, Jinlong Qi, Fan Zhang, Caixia Jia, Li Li, Yani Liu
Professor and Chair, Department of Pharmacology
Hebei Medical University