S18-5 **Selective and direct inhibition of TRPC3 channels underlies biological activities of a pyrazole compound**

◯Yasuo MORI[1], Shigeki KIYONAKA[1], Kenta KATO[1], Motorhio NISHIDA[2], Kazuhiro MIO[3], Chikara SATO[3], Itaru HAMACHI[1]

[1]Kyoto Univ. Grad. Sch. Eng., [2]Kyushu Univ. Grad. Sch. Pharm. Sci., [3]AIST

Canonical transient receptor potential (TRPC) channels control influxes of Ca^{2+} and other cations that induce diverse cellular processes upon stimulation of plasma membrane receptors coupled to phospholipase C (PLC). Invention of subtype-specific inhibitors for TRPCs is crucial for distinction of respective TRPC channels that play particular physiological roles in native systems. Here, we identify a novel pyrazole compound (Pyr3) which selectively inhibits TRPC3 channels. Structure-function relationship studies of pyrazole compounds showed that the trichloroacrylic amide group is important for the TRPC3 selectivity of Pyr3. Electrophysiological and photoaffinity labeling experiments reveal a direct action of Pyr3 on the TRPC3 protein. In DT40 B lymphocytes, Pyr3 potently eliminated the Ca^{2+} influx-dependent PLC translocation to the plasma membrane and late oscillatory phase of B cell receptor-induced Ca^{2+} response. Moreover, Pyr3 attenuated activation of nuclear factor of activated T cells, a Ca^{2+}-dependent transcription factor, and hypertrophic growth in rat neonatal cardiomyocytes, and *in vivo* pressure overload-induced cardiac hypertrophy in mice. These findings on important roles of native TRPC3 channels are strikingly consistent with previous genetic studies. Thus, the TRPC3-selective inhibitor Pyr3 is a powerful tool to study *in vivo* function of TRPC3, suggesting a pharmaceutical potential of Pyr3 in treatments of TRPC3-related diseases such as cardiac hypertrophy.