27O-ISMS16 **Identification of Selective TRPM8 Antagonists for the Treatment of Neuropathic Pain**

○Masashi OHMI[1], Yuji SHISHIDO[1], Kazuo ANDO[1], Kiyoshi KAWAMURA[1], Hiroyuki OHSHIRO[1], Akiyoshi FUJIUCHI[1], Akiko YAMADA[1], Norikazu GAJA[1], Azusa SATO[1], Yumi ISOGAI[1], Shuzo WATANABE[1]
[1]RaQualia Pharma Inc.

The transient receptor potential melastatin 8 (TRPM8) channel is activated by cold temperature (<28°C). TRPM8 channel plays an important role in cold hypersensitivity induced by oxaliplatin, which is a dose limiting toxicities of oxaliplatin-based chemotherapy. We started a research to identify novel TRPM8 antagonists for the treatment of acute neurotoxic effect of oxaliplatin treatment.

We discovered several chemical series via high throughput screening (HTS). As a result of the structure activity relationship (SAR) study to improve solubility and liver microsomal stability, we identified orally available TRPM8 antagonists, RQ-00203078 and RQ-00434739, as preclinical candidates. Both candidates showed potent in vitro activity and high selectivity over other ion channels, receptors, and enzymes. They showed significant inhibition of oxaliplatin-induced cold allodynia in the rats. Furthermore, RQ-00434739 (10 mg/kg p.o.) fully reversed oxaliplatin-induced cold allodynia in the monkeys.

These results support clinical development of RQ-00203078 and RQ-00434739 as potential therapy for acute symptoms in oxaliplatin-treated patients.