

# Volume-regulated anion channel VRAC as a target in drug discovery

Reference Number: 03-00389

## Challenge

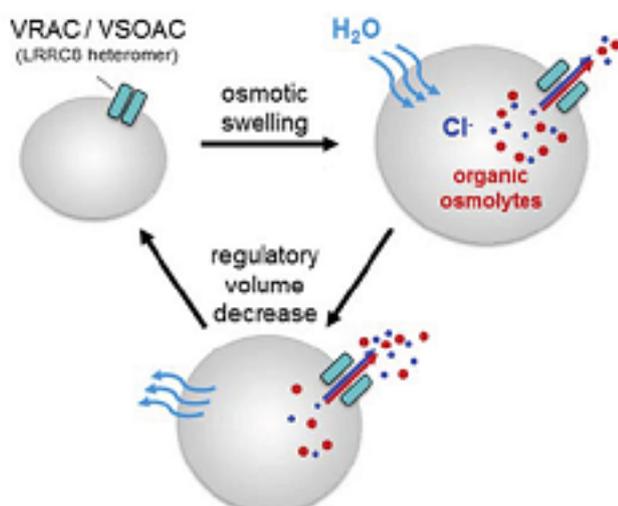
The regulation of the cell volume plays an integral role in a broad variety of physiological processes. Upon swelling of cells due to e.g. osmotic pressure, regulatory volume decrease (RVD) is induced by release of potassium, chloride anions and organic osmolytes, leading to the release of water. Conductance of these ions and osmolytes is performed by the volume-regulated anion channel VRAC which is opened upon swelling of the cell. VRAC inhibitors have been shown to reduce ischemic events such as brain damage since ischemia in e.g. heart and brain is accompanied by an increase of cell volume. Furthermore, VRAC may have a distinct role in cancer due to its function during proliferation, cell cycle progression and cell migration. VRAC is also linked to programmed cell death where apoptotic volume decrease takes place. Studies point to a correlation of VRAC activity with cis-platin resistance during cancer treatment. Thus, potent and selective VRAC modulators do have the potential to address novel pathways in a broad variety of diseases.



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VRAC regulates cell volume by regulatory volume decrease upon osmotic swelling.

## **Technology**

The technology provides VRAC as a target in drug discovery and means to screen for selective modulators of the VRAC ion channel. For more than twenty years, the molecular identity of the VRAC ion channel was unknown. Recently this long lasting search resulted in the discovery that proteins of the LRRC8 family form essential components of this ion channel. RNAi knock-down experiments identified LRRC8A as a key protein for VRAC functionality. Further experiments revealed the role of LRRC8A and the remaining members LRRC8B-LRRC8E in the formation and function of heteromeric complexes as VRAC components. Due to the close resemblance to the ion channel families of pannexins, LRRC8 proteins are assumed to form heterogenic hexamers with LRRC8A as an indispensable sub-unit. The formation of VRAC species with different LRRC8B-LRRC8E components would allow for diverse VRAC channels with specific cellular functions. Thus, the development of selective modulators of this ion channel may pave the way to novel treatments in several disease areas such as cancer or in ischemic incidents.

## **Commercial Opportunity**

Available for licensing or collaboration

## **Patent Situation**

Patent applications pending in Europe (EP 14172703) and USA (US 14/642,776)

## **Further Reading**

Voss et.al., Science, 344(6184), 634-638

Qiu et.al., Cell, 157(2), 447-458

Stauber et.al, Biol Chem. 2015 Apr 11