Docket #: S17-473

High-affinity, small-molecule, CLC-2 chloride ion channel probes

Stanford researchers developed a first-in-class small-molecule inhibitor of the CLC-2 ion channel for research and drug development. CLC-2 is part of the CLC family of chloride ion channels, which regulate the flux of chloride ions across cell membranes. These proteins play critical roles in electrical signaling of muscles and neurons and in maintaining proper water and salt balance throughout the body. Existing classes of CLC inhibitors have been poor drug candidates, as they lack isoform selectivity and have low potency against their intended targets.

To address this problem, Stanford researchers have developed a low-nanomolar potency (14 nM), small-molecule inhibitor of the CLC-2 chloride channel with demonstrated specificity for its target within the central nervous system (CNS). Specificity has been validated with a genetic knockout model, as well as through screening against a panel common CNS channels, receptors, and transporters. Of particular interest is the role of CLC-2 in brain diseases, such as epilepsy, leukoencephalopathy, and glioma cancers. Other potential disease applications include treatment of aldosteronism (a common cause of high blood pressure) and intestinal disorders (such as irritable bowel syndrome). This CLC inhibitor can serve as valuable pharmacological tool for neuroscience, physiology studies, and development of new therapeutic leads for CLC-2-related disease.

Stage of Development - Ex Vivo Proof of Concept
Research is ongoing to improve compound affinity and selectivity, and to develop molecules into imaging probes.

Applications

- Drug research and development - aldosteronism, and central nervous system diseases like epilepsy, leukoencephalopathy, and gliomas

    - Pharmacological tool
    - Therapeutic leads

Advantages

- First-in-class, small-molecule (non-peptide) modulators
- High affinity, selectivity, and specificity

Publications

- Koster, Anna K., Austin L. Reese, Yuri Kuryshev, Xianlan Wen, Adam C. Lu, Keri A. McKiernan, Erin E. Gray Caiyun Wu, Mark P. Beenhakker, John R. Huguenard, Merritt Maduke, J. Du Bois. "Development and validation of a potent and specific inhibitor provides evidence for the CLC-2 chloride channel as a potential epilepsy target." *bioRxiv* (2020).
- Koster, Anna K., Justin Du Bois, and Merritt C. Maduke. "Compositions and methods to modulate chloride ion channel activity." U.S. Patent Application 16/449,021, published January 16, 2020.
- Koster, Anna Katherine. "Expanding the Small-molecule Toolbox for Studying CLC Chloride Channel Physiology and Biophysics." PhD diss., Stanford University, 2019.

Patents

- Published Application: 20200016103
- Issued: 11,173,137 (USA)

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