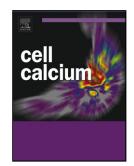
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# ACCEPTED MANUSCRIPT

#### Review

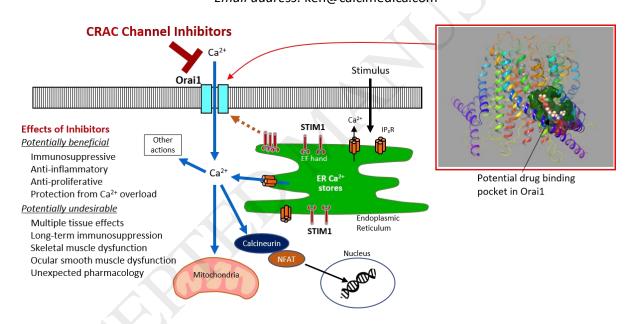
### **CRAC Channels as Targets for Drug Discovery and Development**

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 $Ca^{2+}$  release from the endoplasmic reticulum (ER) is triggered by the opening of IP<sub>3</sub> receptors (IP<sub>3</sub>R) or by other means. The resulting decrease in ER Ca<sup>2+</sup> levels is sensed by STIM1, which then oligomerizes and gates Orai1 in the plasma membrane. Ca<sup>2+</sup> entry via Orai1-containing CRAC channels can activate intracellular signaling pathways and can be pharmacologically blocked by inhibitors, resulting in potentially beneficial or undesirable effects. An image of a potential binding pocket in Orai1 for CRAC channel inhibitors is shown at right, showing the drug-bound pocket superimposed on the crystal structure of Orai1.

Highlights of Review by Kenneth A. Stauderman

- Numerous high-throughput screens or other approaches have identified CRAC channel modulators
- For these compounds to advance, potency, selectivity, efficacy, pharmacokinetic, safety, and toxicological concerns must be addressed
- Orai1 and STIM1 are currently the most attractive CRAC channel components to target
- A handful of potent and selective CRAC channel inhibitors have now reached clinical trials in humans

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