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Low-Power Optogenetic Excitation and Suppression of Human Ventricular Cardiomyocytes Expressed with ChRmine and HcKCR1

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OBJECTIVE

To design a novel method for efficient optogenetic control of Human Ventricular Cardiomyocytes (HVCMs) with newly discovered ChRmine and HcKCR1 Channelrhodopsins.

CARDIAC OPTOGENETICS

Technique for controlling genetically modified HVCMs with light.

Importance

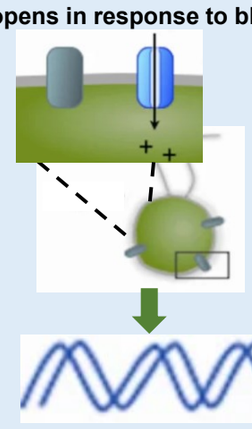
- *Revolutionary Technique*
- *Relatively Low Invasiveness*
- *High Spatiotemporal Resolution*

Applications

- *Cardiac Electrophysiology*
- *Restoring Pacemaking Ability*
- *Terminating Cardiac Arrhythmias*

Mechanism

Protein is an ion channel that opens in response to blue light.

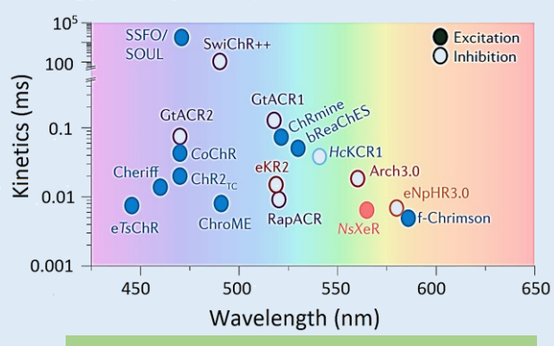


Take the gene for this protein.

Opsin-expressed in rat neuron for controlling neural activity with light.

Insert the DNA into specific neurons in the brain.

Excitation and Inhibition depends on, which type of Opsin expressed into the cells.



Channelrhodopsins in Optogenetics

Deisseroth K., *Nat. Neurosci.* 18, 1213–1225, 2015
Emiliani V. *et al.*, *Nat. Rev. Methods Primers* 2, 2022.

Recent Study (2023)

Optical Pacing with ChRmine-expressing Rat Cardiomyocytes

Article | Open Access | Published: 01 March 2023

Cardiogenic control of affective behavioural state

Brian Hsueh, Ritchie Chen, YoungJu Jo, Daniel Tang, Misha Raffiee, Yoon Seok Kim, Masatoshi Inoue, Sawyer Randles, Charu Ramakrishnan, Sneha Patel, Doo Kyung Kim, Tony X. Liu, Soo Hyun Kim, Longzhi Tan, Leili Mortazavi, Arjay Cordero, Jenny Shi, Mingming Zhao, Theodore T. Ho, Ailey Crow, Ai-Chi Wang Yoo, Cephra Raja, Kathryn Evans, Daniel Bernstein, ... Karl Deisseroth + Show authors

Nature **615**, 292–299 (2023) | Cite this article

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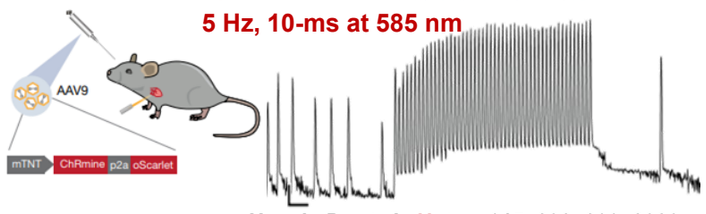
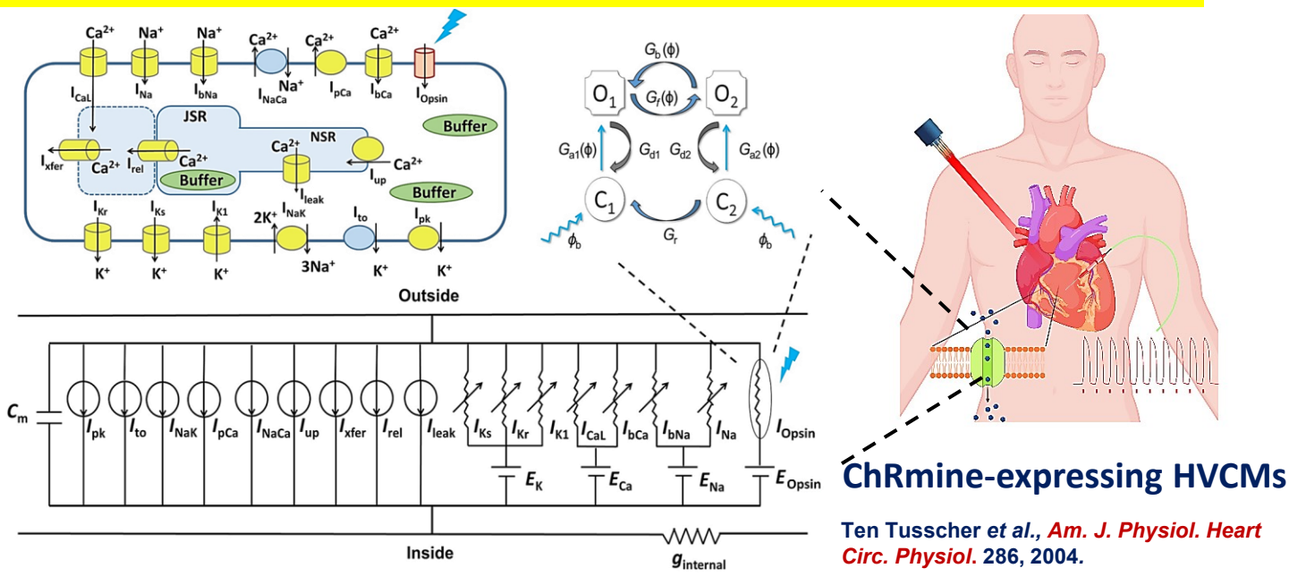


Hsueh D. *et al.*, *Nature* **615, 292–299, 2023.**

THEORETICAL MODEL

Model of Opsin-expressing Human Ventricular Cardiomyocytes



ChRmine-expressing HVCMs

Ten Tusscher *et al.*, *Am. J. Physiol. Heart Circ. Physiol.* 286, 2004.

Photocurrent

$$I_{Opsin} = g_{opsin}\,(O_1 + \gamma O_2)(V - E_{Opsin})$$

Equilibrium condition

$$C_1 + O_1 + O_2 + C_2 = 1$$

Rate equations

$$\dot{O}_1 = G_{a1}(\phi)C_1 + G_b(\phi)O_2 - \left(G_{d1} + G_f(\phi)\right)O_1 \qquad \dot{C}_1 = G_{d1}O_1 + G_rC_2 - G_{a1}(\phi)C_1$$

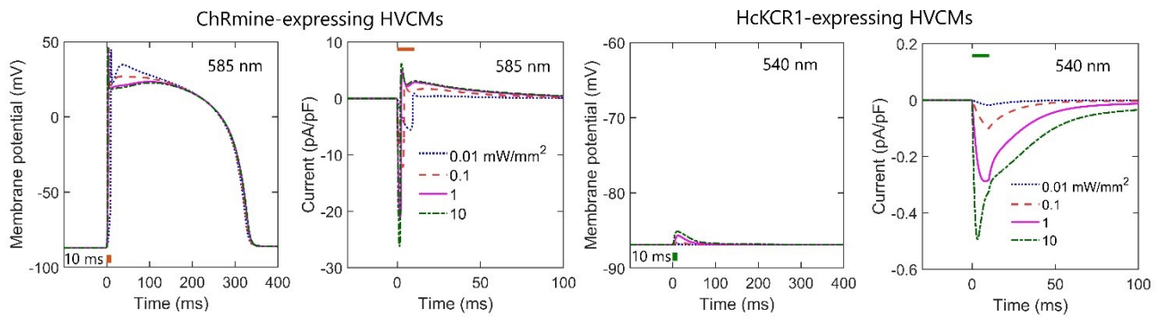
$$\dot{O}_2 = G_{a2}(\phi)C_2 + G_f(\phi)O_1 - \left(G_{d2} + G_b(\phi)\right)O_2 \qquad \dot{C}_2 = G_{d2}O_2 - (G_r + G_{a2}(\phi))C_2$$

Rate of Change in membrane potential

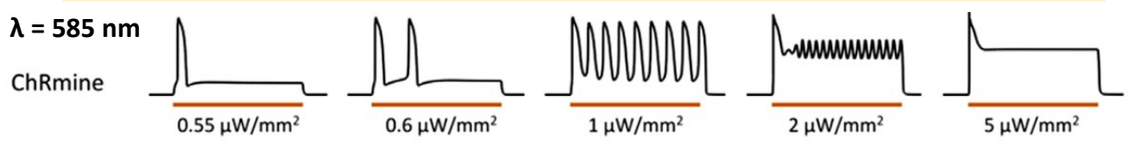
$$C_m\dot{V} = -I_{opsin} - I_{stim} - (I_{Na} + I_{to} + I_{K1} + I_{Kr} + I_{Ks} + I_{NaK} + I_{pK} + I_{NaCa} + I_{pCa} + I_{bCa} + I_{bNa} + I_{up} + I_{leak} + I_{rel} + I_{xfer} + I_{CaL})$$

RESULTS & DISCUSSION

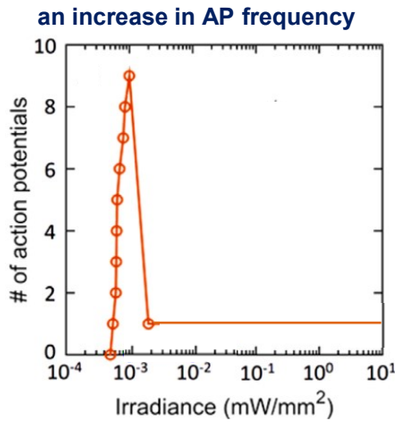
Effect of Irradiance on Membrane Potential and Photocurrent



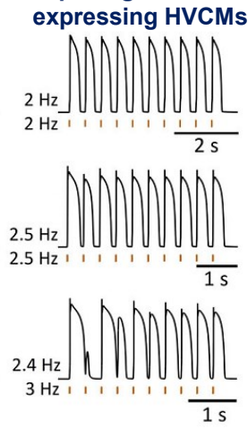
Effect of Continuous and Pulsed Optical Illumination



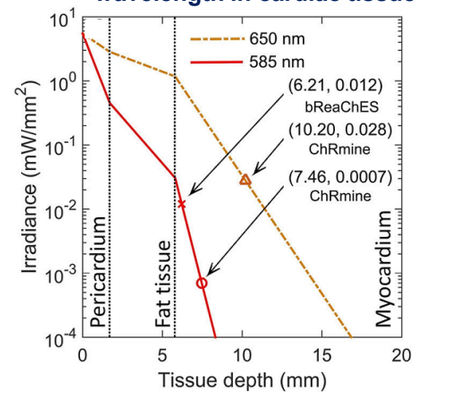
Increase in irradiance results in an increase in AP frequency



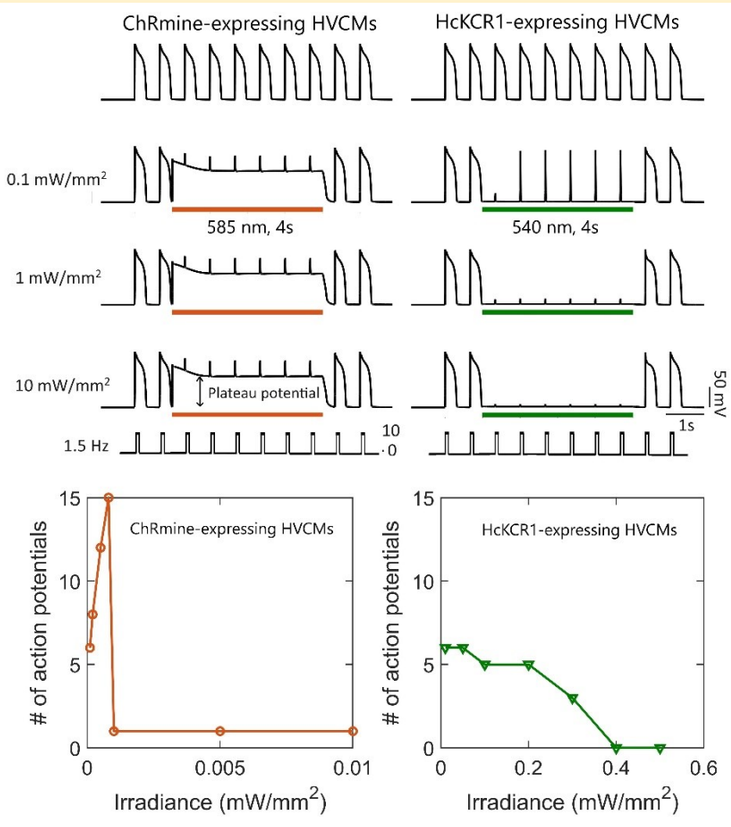
Optical pacing with ChRmine-expressing HVCMs



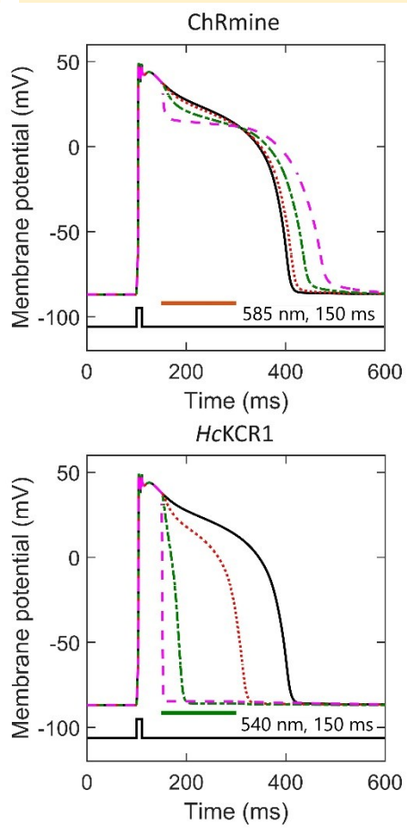
Activable tissue depth at different wavelength in cardiac tissue



Suppression of Electrically-Evoked APs



Shortening of APD



CONCLUSION

- **Formulated accurate theoretical models of optogenetic excitation and suppression of cardiac activity in HVCMs.**
- **Useful for designing compact, low-cost optical pacemaker.**
- **Upgraded to tissue and organ scales for getting pre-clinical insights.**

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