Docket #: S06-457

Cell Line for Optically-based Screening of Ion Channel Modulators

Ion channel dysfunctions lead to a wide array of illnesses including epilepsy, cardiac arrhythmia and type II diabetes. However, the number of clinically approved drugs for restoring normal ion channel function is limited. A major bottleneck for the development of new ion channel drugs is that present screening methodologies are primarily based on patch clamping, a powerful, but time consuming technique that only allows examination of only a handful of compounds a day. Stanford University scientists have developed a concept system for high-throughput screening of ion channel drugs using optical stimulation and fluorescent read-out.

In this system, light of the proper wavelength is cast upon the optically-gated cells in each well in the presence of a novel compound, the cells will react or fail to react to the light, based upon the drugs' properties. To create this system, a light sensitive ion channel (e.g. *Chlamydomonas* channelrhodopsin-2 and *Volvox* channelrhodopsin-1) and a voltage-gated Ca2+ channel are co-expressed in 293T cells. Upon illumination with the appropriate wavelength of light, light-mediated depolarization activates the co-expressed voltage-gated Ca2+ channels. The subsequent activity of Ca2+ channel in the presence of different small molecules is the optically monitored using either a fluorescent indicator dye (i.e. Fura-2) or genetically encoded activity sensor. The fluorescence signal is recorded via time-lapse imaging for later analysis.

Applications

- High-throughput screening for therapeutics that target ion channels

Advantages

- Improved screening throughput by eliminating the need for cumbersome mechanical manipulation and liquid handling
- Added ability to repeat the screening assay using the same samples
- Reduced screening cost by eliminating the need for chemically-based fluorescence reporters
- High temporal precision and low signal artifact since all of the voltage manipulation is accomplished optically
- Ability to modulate the level of depolarization by attenuating the light intensity used for stimulation
- Ability to look at kinetics of the drug's modulation on the ion channel using pulsed light patterns

Publications

- US Patent Application: 12/187,927
- Schneider MB, Gradinaru V, Zhang F, Deisseroth K. Controlling Neuronal Activity. Am J Psychiatry. 2008 May;165(5):562.

Patents

- Published Application: 20090099038
- Published Application: 20130288365
- Published Application: 20160258929
- Published Application: 20200072817
- Issued: 10,451,608 (USA)

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