REVOLUTIONARY OPTOGENETIC TECHNOLOGY

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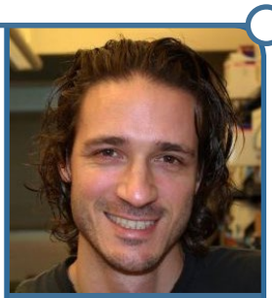
Modulating the nervous system with light to transform disease treatment



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The need for novel approaches in CNS drug discovery for psychiatric and neurological diseases

There is a large unmet need worldwide for novel therapies in CNS diseases. Neuropsychiatrict diseases such as major depressive disorder, schizophrenia, autism, and anxiety impose a huge socio-economic burden on society and millions of affected patients are suffering from the debilitating symptoms of these conditions. However, the underlying disease mechanisms are still not well understood and current treatments provide limited relief. The three major classes of psychiatric drugs (anti-psychotic D2 antagonists, anxiolytic GABA receptor agonists and antidepressant monoamine reuptake inhibitors), have limited efficacy in reducing and controlling symptoms, and are often accompanied by significant side effects. Very few new treatments for neuropsychiatric conditions have entered the market during the last few decades and none have transformed treatment in any meaningful way. It is also becoming apparent that psychiatric diseases might be best viewed as spectrum disorders with defined combinations of symptom domains, rather than as monotonic disease states. Moreover, classical preclinical models of neuropsychiatric symptoms have not proven to be predictive of clinical outcomes. Using a combination of in vivo optogenetics, behavioral profiling and a proprietary single cell transcriptomics platform, Circuit Therapeutics has been able to dissect the neural circuitry that underlies specific symptoms and identify specific novel therapeutic targets that modulate those circuits.

What is optogenetics?

Optogenetics is a transformational technology that enables exquisite control of specific neurons and modulate their activity using a directed light source. With optogenetics, we can selectively control neuronal firing patterns in awake and behaving animals and gain insights into how a neuronal circuit influences behavior in normal and disease states. Optogenetics requires two key components: A light-sensitive protein, or opsin, and a light source. Depending on the wavelength, light can either activate neurons with excitatory opsins (e.g., channelrhodopsin), silence neurons with inhibitory opsins (e.g., halorhodopsin), or initiate cellular signaling cascades (e.g., OptoXR). Adjusting the location, strength and wavelength of the light allows for exacting control of the opsin activity. Furthermore, opsins can be selectively delivered to specific cell types. For example, cells with defined expression patterns within a given brain region can be targeted using localized delivery along with discerning expression strategies that harness cell type-specific promoters or transgenes. The opsin toolbox thus provides great flexibility and high specificity for modulating neuronal activity in vivo. By activating or inhibiting individual circuits in the central and peripheral nervous systems, we can alter neuronal activity, animal behavior, and model a specific disease symptom. This unique insight into how individual circuits contribute to symptoms or disease states enables the discovery of novel therapeutics.

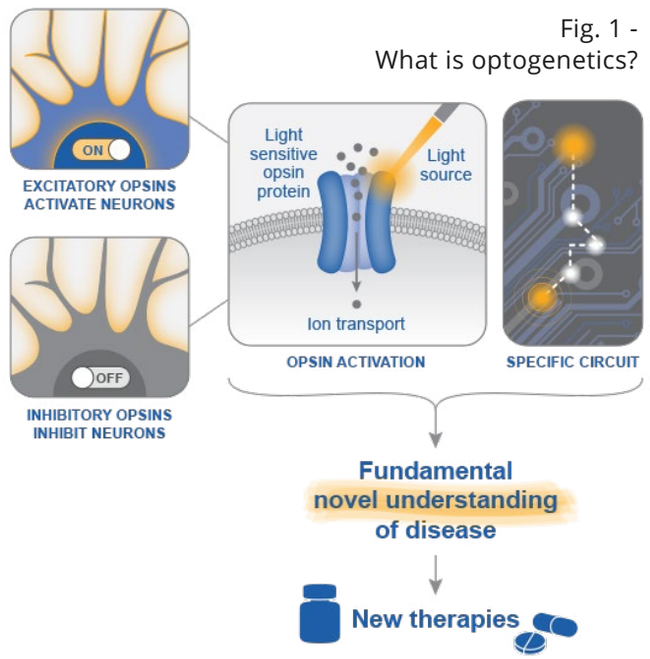

Fig. 1 - What is optogenetics?

Optogenetic Drug Discovery

Using optogenetics, we can identify the neuronal circuits that are responsible for behavioral symptoms of specific neuropsychiatric disease. Combining optogenetics with single-cell transcriptomics enables us to characterize the gene expression profiles of the neurons that are responsible for a given neuropsychiatric symptom. Finally, using the insights we gain into the symptomatic etiology of the disease and the molecular targets that associate with with symptoms, we can develop unique therapies with unprecedented efficacy. Optogenetics facilitates new ways to approach drug discovery and development for the treatment of brain disorders ■

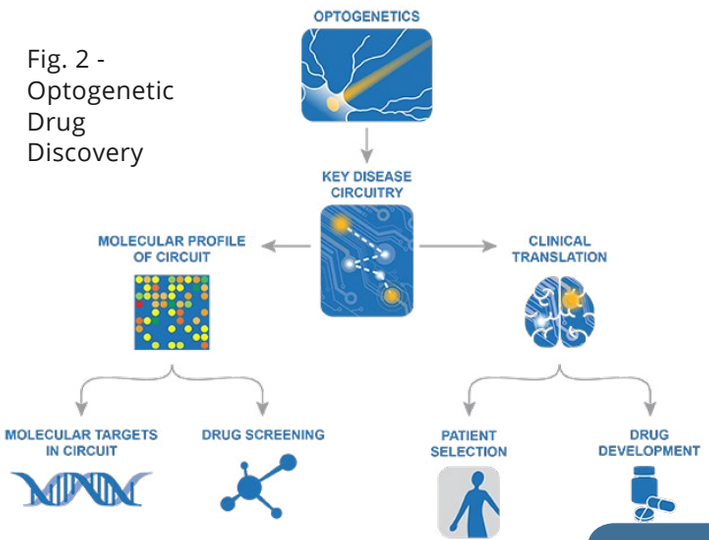

Fig. 2 - Optogenetic Drug Discovery