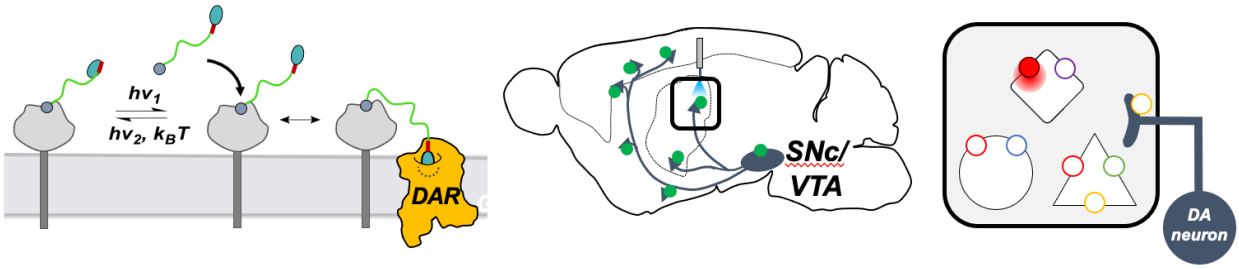
Isacoff Lab-UC Berkeley: Cell specific optical control of dopamine receptors



Dopamine controls diverse behaviors whose dysregulation contributes to motor, cognitive, sleep and mood disorders. Our ability to understand and manipulate the function of dopamine is limited by the heterogenous nature of dopaminergic projections, the diversity of neurons that are regulated by dopamine, the varying distribution of the five dopamine receptors (DARs), and the complex dynamics of dopamine release. To specifically modulate particular DARs in select cells, we are developing a photo-pharmacological strategy using Photoswitchable Orthogonal Remotely Tethered Ligands (PORTLs).

We initially developed PORTLs to remote control engineered metabotropic glutamate receptors (mGluRs) and DARs that are fused to a protein tag (SNAP, CLIP or HALO) to which the PORTL attaches (Broichhagen, *ACS Central Science* 2015; Donthamsetti, *JACS*, 2017) and have used SNAP-mGluR2 in the mouse retina for vision restoration (Berry et al., *Nature Com.* 2017). We recently adapted the approach to control native receptors by expressing in select cells a membrane anchor protein (M) to which the PORTL attaches (to generate an M-P). The M-P diffuses in the cell or can be targeted to a specific subcellular location (e.g. pre- or post-synaptically) to find the receptor to which it presents the PORTL. We initially did this for mGluRs (Donthamsettti, *JACS* 2019). We recently described a first D1R/D5R receptor agonist (MP-$D1_{ago}$) whose photo-activation in medium spiny neurons promotes movement initiation in the dorsal striatal but not in the nucelus accumbens (Donthamsetti, *Nature Com*, 2021).

In new work, we have generated a D1 photo-antagonist, a D2 photo-agonist and D2 photo-antagonist. The goal of the project is to characterize these photoswitches and others that are in-production, and employ them to study dopamine modulation of synaptic transmission, circuit function and behavior in one of several systems: cultured mammalian neurons and brain slice, zebrafish prey capture circuit, mouse striatum.

The work in the striatum is motivated by the conception that photo-activation of specific DARs in select striatal cells can substitute for loss of dopaminergic input as dopaminergic neurons degenerate. We will test this in animal models of Parkinson's Disease with the idea of developing a treatment for late-stage disease that substitutes for the normal signal and so is more specific and effective than deep brain stimulation.

We seek a motivated postdoc with experience in electrophysiology. Knowledge of fluorescence spectroscopy and/or behavior is a plus. The candidate will work alongside molecular biophysicists studying metabotropic and ionotropic glutamate receptors, neuroscientists performing super-resolution quantal imaging of synaptic transmission in Drosophila and mammalian neurons, and vision scientists employing photo-activated receptors for vision restoration.

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