A cell-based screen for inhibitors of flagella-driven motility in Chlamydomonas reveals a novel modulator of ciliary length and retrograde actin flow

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Cilia are motile and sensory organelles with critical roles in physiology. Ciliary defects can cause numerous human disease symptoms including polycystic kidneys, hydrocephalus, and retinal degeneration. Despite the importance of these organelles, their assembly and function is not fully understood. The unicellular green alga Chlamydomonas reinhardtii has many advantages as a model system for studies of ciliary assembly and function. Here we describe our initial efforts to build a chemical-biology toolkit to augment the genetic tools available for studying cilia in this organism, with the goal of being able to reversibly perturb ciliary function on a rapid time-scale compared to that available with traditional genetic methods. We screened a set of 5520 compounds from which we identified four candidate compounds with reproducible effects on flagella at nontoxic doses. Three of these compounds resulted in flagellar paralysis and one induced flagellar shortening in a reversible and dose-dependent fashion, accompanied by a reduction in the speed of intraflagellar transport. This latter compound also reduced the length of cilia in mammalian cells, hence we named the compound ”ciliabrevin” due to its ability to shorten cilia. This compound also robustly and reversibly inhibited microtubule movement and retrograde actin flow in Drosophila S2 cells. Ciliabrevin may prove especially useful for the study of retrograde actin flow at the leading edge of cells, as it slows the retrograde flow in a tunable dose-dependent fashion until flow completely stops at high concentrations, and these effects are quickly reversed upon washout of the drug.

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