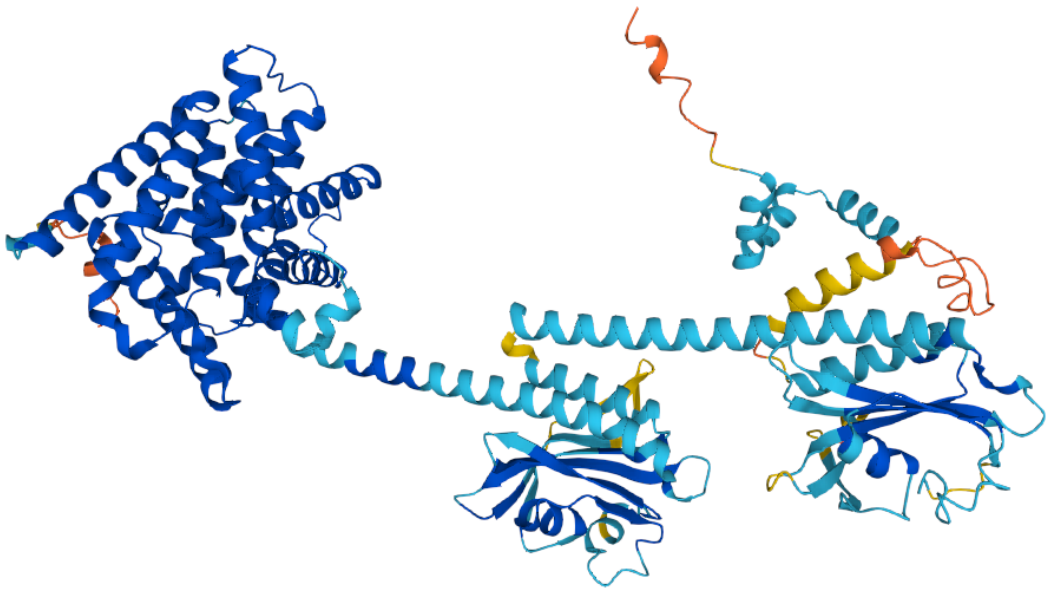
CellarisBio

PDE10

Phosphodiesterase 10 (Homo sapiens)



Case study

V1.0

About PDE10

PDE10 (Phosphodiesterase 10) is an enzyme that plays a crucial role in intracellular signaling pathways by regulating the levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). It is predominantly expressed in the brain, particularly in the striatum, where it modulates dopaminergic and glutamatergic signaling pathways. Research suggests that dysregulation of PDE10 activity is implicated in various neurological and psychiatric disorders, including Huntington's disease, schizophrenia, and Parkinson's disease.

1. **Huntington's Disease (HD):** HD is a neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and psychiatric symptoms. PDE10 inhibitors have shown therapeutic potential in preclinical models of HD by increasing cAMP and cGMP levels, which may help mitigate the pathological effects associated with HD.
2. **Schizophrenia:** Alterations in dopaminergic and glutamatergic neurotransmission are implicated in schizophrenia. PDE10 inhibitors have been investigated as potential antipsychotic agents due to their ability to modulate these neurotransmitter systems. By inhibiting PDE10 and consequently increasing cAMP and cGMP levels, these inhibitors may help restore neurotransmitter balance and alleviate schizophrenia symptoms.
3. **Parkinson's Disease (PD):** PD is characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to motor impairments. PDE10 inhibitors have shown neuroprotective effects in preclinical models of PD by enhancing cAMP and cGMP signaling, which may promote neuronal survival and function.

PDE10 appears to be a promising target for therapeutic intervention in various neurological and psychiatric disorders. Further research is needed to elucidate the specific mechanisms underlying PDE10 dysregulation in these conditions and to develop effective PDE10-targeted therapies.

Therapeutic challenges of PDE10

Several challenges have been encountered in targeting PDE10 for therapeutic purposes:

1. **Selectivity**: PDE10 is part of a larger family of enzymes, and achieving selectivity for PDE10 over other phosphodiesterases can be challenging.
2. **Blood-Brain Barrier (BBB) Penetration**: Developing compounds that can effectively cross the BBB while maintaining PDE10 selectivity is a significant challenge.
3. **Safety Profile**: Modulating PDE10 activity may impact various physiological processes beyond the intended therapeutic target.
4. **Efficacy**: Despite promising preclinical findings, translating efficacy from animal models to human patients remains challenging.
5. **Disease Complexity**: Neurological and psychiatric disorders are often multifaceted, involving complex interactions between various molecular pathways and cellular processes.

Targeting PDE10 with MICRO-TAG target[2] engagement system

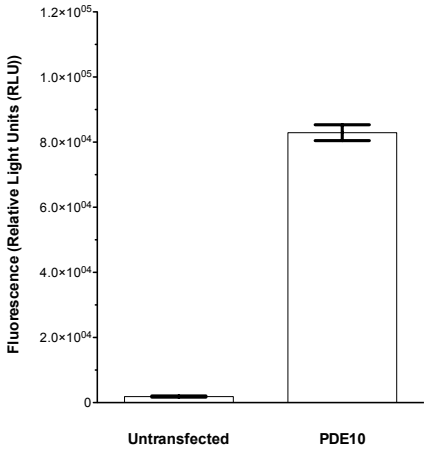
CellarisBio MICRO-TAG target engagement technology is ideal for discovering novel compounds that bind PDE10 to modulate its activity. Steps involved to develop this assay system:

Step 1: Design a MICRO-TAG reporter for the target.
Step 2: Establish thermal melting profile of the target.
Step 3: Run a pilot test with a reference compound.
Step 4: Scale the system for compound discovery.

Step 1: Design MICRO-TAG reporter specific for PDE10

DNA construct encoding for PDE10 transfected into HEK293 cells MICRO-TAG system works on the basis of enzyme complementation that generates fluorescence signal. Hence, following satisfactory expression of the target, enzyme complementation of the MICRO-TAG construct is tested, as shown in **Figure 1**.

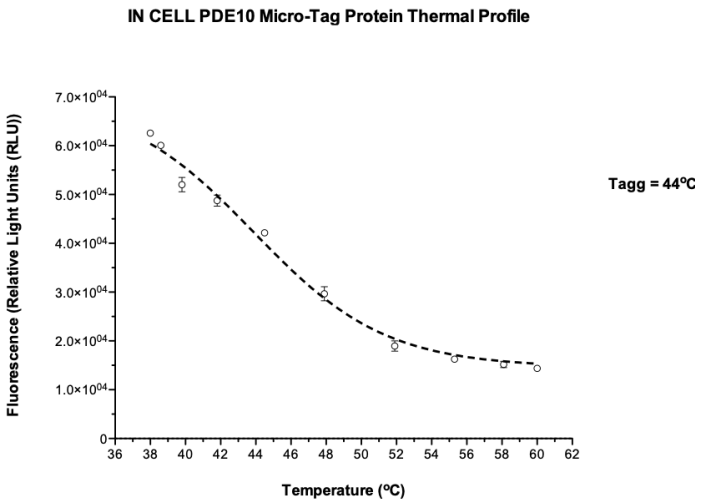
Figure 1: Activity of MICRO-TAG target construct for PDE10.



Step 2: Establish the thermal melting profile

Once the quality control for the reporter construct has passed then the next step is to determine the temperature at which to interrogate ligand binding. A thermal profile of the target is established by applying a thermal gradient to the cells expressing the target (**Figure 2**). From this thermal profile a temperature of aggregation ($T_{agg}50$) is determined at which 50% of the target is in the unfolded and denatured/aggregated state.

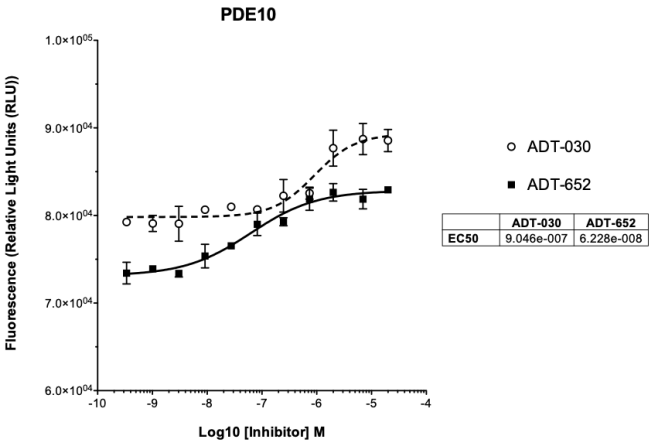
Figure 2: Step 2 – Establish Thermal Melting Profile



Step 3: Run a pilot test with a reference compound

$T_{agg}50$ is the temperature point at which ligand binding to the target is tested. When a ligand binds it alters the conformation of the target and promotes stability of the target within a thermal challenge. This is the concept of thermal shift assay. For the PDE10 MICRO-TAG assay reporter system an assay optimization strategy involves reference compounds that have been demonstrated to bind to the target. Binding of the compound to PDE10 within a heat challenge stabilizes the target resulting in an increase in fluorescence signal from the stabilized PDE10 (**Figure 3**).

Figure 3: Step 3 – Cell target engagement of reference compound with PDE10.



The pilot phase also provides an opportunity to optimize the assay to capture more response from the cellular drug-target engagement.

Step 4: Scale the system for compound discovery

Once the pilot step is accomplished, the reporter assay is ready for scale-up. Depending on requirements, there are several options to consider.

Transient expression of the MICRO-TAG target can be used for low-throughput screens aiming at validation of advanced drug candidates. Stable MICRO-TAG reporter assay can be generated using lentiviral knock-in or CRISPR approach. This latter approach is more tuned for high-throughput primary screens aimed at discovering of novel candidates.

Accelerate and De-Risk Drug Discovery with CellarisBio

CellarisBio's is a drug discovery technology company, based in San Diego, California. Our MICRO-TAG cell target engagement platform is built to tackle challenging drug targets.

We work across various therapeutic targets classes such as:

- Enzymes
- Membrane proteins
- Transcription factors
- Other challenging proteins

We work with multiple therapeutic modalities such as:

- Small molecules
- Peptide
- PROTACS
- Antibodies

Accelerate your drug discovery with CellarisBio:

- Discover drug candidates using DNA-Encoded Libraries or plated libraries,
- Validate drug candidates for potency and selectivity,
- Analyze for in-cell kinetics and live-cell imaging.

Some of the drug targets we worked with:

What drug targets are you interested in?

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