Docket #: S17-337A

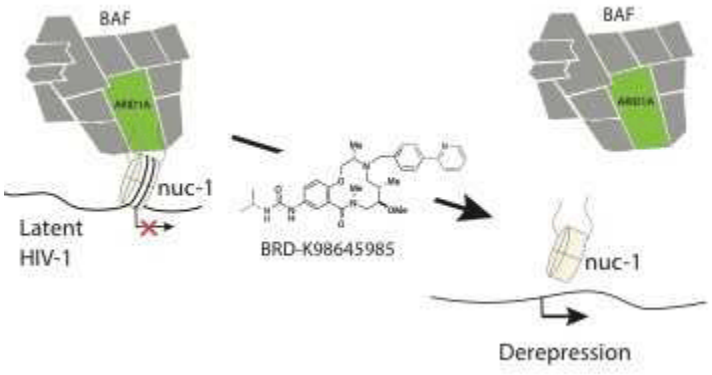
HIV Latency Reversal Agents that target Chromatin remodeler-driven repressive HIV promoter structure

Disease indication - HIV infection, specifically reversal of viral latency alone or in combination with other latency reversal agents to improve reservoir targeting.

Drug format - Small molecule: new scaffold for family of novel compounds with a 12-membered macrolactam.

Drug class - First-in-class of latency reversal agents.

Research stage and Preliminary data –
Target validation: The inventors demonstrated the effects of these molecules on HIV latency in both an in vitro T cell line and an ex vivo primary cell model of HIV-1 latency. Results showed no toxicity or T cell activation.
Target identification and Structure-activity Relationship: The inventors demonstrated the specific sub-unit targeted by the macrolatam scaffold and optimized its activity.



Target - These molecules target BAF (mammalian SWI/SNF) chromatin remodeling complex through the BAF-specific subunit ARID1A. BAF is involved in establishing and maintaining viral latency through nucleosome positioning.

Background - Patients with HIV-1 infections are currently treated with combination Anti-Retroviral Therapy (cART) which is extremely effective at suppressing HIV-1 to undetectable levels and preventing progression to AIDS. However, cART therapy does not entirely eliminate the virus due to a pool of latently infected cells that persist in the body. This viral reservoir presents a major roadblock to curing HIV infection and therefore patients must maintain cART therapy for life.

A number of genetic and epigenetic factors establish and maintain latency. Chemically targeting these regulators with the aim to purge the latent reservoir could provide a cure. However, to date, latency reversal agents (LRAs) have been hampered by limited effectiveness or high toxicity, stressing the need for more specific and less toxic compounds. These new LRA agents are selective and non-toxic and could present an avenue to eliminate latent HIV infection to potentially cure the disease without further cART treatment.

Mode of action - The BAF (mammalian SWI/SNF) chromatin remodeling complex is involved in establishing and maintaining viral latency through nucleosome positioning which represses HIV-1 Tat mediated transcription. Target identification experiments implicate ARID1A (a BAF-specific subunit) as the primary target. These molecules target the BAF-specific subunit ARID1A to prevent nucleosomal positioning, relieving transcriptional repression of HIV-1 and reversing latency.

Related Technology - These compounds could also be used to treat cancer (see Docket S17-337).

Advantages

- **Low toxicity** - compound identified in screen for drugs that inhibit BAF-mediated transcription without affecting cellular viability, thereby reducing the chance for side effects
- **Specific target** - selectively targets ARID1A subunit of BAF complex
- **Enhances the activity** of other latency reversal agents, such as those targeting HDACs (histone deacetylases) and PKC (protein kinase c)

Publications

- Marian, C. A., Stoszko, M., Wang, L., Leighty, M. W., Crignis, E. D., Maschinot, C. A., . . . Dykhuizen, E. C., “Small Molecule Targeting of Specific BAF (mSWI/SNF) Complexes for HIV Latency Reversal,” *Cell Chemical Biology*, (2018) doi:10.1016/j.chembiol.2018.08.004

Patents

- Published Application: WO2020014524
- Published Application: 20210315876
- Issued: 11,980,613 (USA)

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