Docket #: S17-337

Hyper-Lethal Combination: Inhibiting Chromatin Remodeling as Cancer-Killing Strategy

Disease indication - Cancer, specifically:
-highly mutated cancers, including the ~20% of cancer with BAF complex mutations
-combination therapy with ATR inhibitors

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

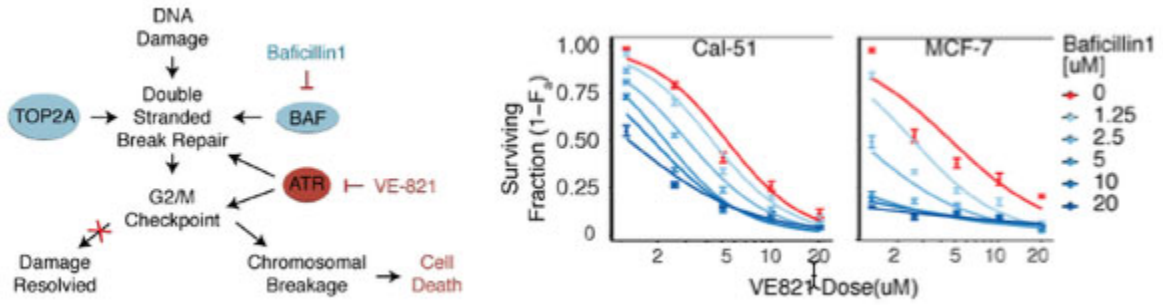
Drug class - First-in-class:
-previous compounds that target this complex (SWI/SNF or BAF) either had no measurable effects on inhibiting the growth of cancer cells or had limited utility in mammals
-first to target BAF complex beyond the ATP-ase subunit

Research stage and Preliminary data - Validation in vitro:
The inventors have tested Baficillin1 and other compounds consisting of a similar backbone in breast and colon cancer cell lines for reductions in cell survival and synergy with the ATR inhibitor VE821. This demonstrated that combining the BAF inhibitor compounds ATR kinase inhibitors leads to hyper synthetic lethal effects. These effects were seen even in non-BAF mutated cancer cells, particularly in highly mutated cell lines, despite the relatively non-toxic effects of Baficillin1 independently.

Target - These molecules selectively inhibit human SWI/SNF (BAF) chromatin remodeling complexes with ARID1A.

Background - SWI/SNF (BAF) chromatin remodeling complexes regulate transcription, replication and DNA repair through a variety of mechanisms. Subunits of the BAF complex are mutated in about 20% of human cancers. Inhibitors of ATR

kinase (Ataxia-Telangiectasia Mutated and Rad3-related protein kinase) have recently been shown to induce a synthetic lethal function in cancer cell lines deficient in the ARID1A subunit of the BAF complex. These new macrolactam molecules were identified in a screen for mammalian SWI/SNF inhibitors that function synergistically with ATR/ATM kinase inhibitors.



BAF/ATR pathway and results in cancer cell lines. *Pathway breakdown illustrating the effects of BAF and ATR inhibition that lead to cell death. Graphs show survival of the cancer cell lines Cal-51 and MCF-7 (Breast Cancer Cell lines) treated with ATR inhibitor VE821 alone or in combination with Baficillin1 over 5 days.*

Mode of action - Results suggest that selectively inhibiting BAF complexes in the presence of ATR inhibitors forces cells into mitotic catastrophe and subsequent cellular arrest. Therefore, this may serve as a viable therapeutic strategy in certain cancers. In particular, the new BAF inhibitors could sensitize aggressive, high-mutated, or potentially drug resistant cancers to a host of chemotherapeutics. This strategy may be effective not only in cancers that have acquired BAF complex mutations, but also in highly mutated cancers which have evolved mechanisms to bypass important DNA damage checkpoints. Since Baficillin1 is not toxic, synergy studies suggest that they may enhance ATR inhibitor activity without additional toxicity to patients.

Related Technology - These compounds could also be used to treat HIV latency (see Docket S17-337A)

Applications

- Cancer treatments for use in combination with ATR inhibitors.

Advantages

- **Low toxicity** - Baficillin1 and other compounds with a shared backbone are non-toxic on their own:
  - reduces chance for side effects
  - in combination therapy, could reduce the dose of ATR inhibitors 10-fold
- **Stronger cell death response**
- **Specific target** - selectively targets ARID1A subunit of BAF complex
- **Tunable features** - primary backbone structure could be chemically modified to the increase potency, bioavailability and stability of the primary molecule

Publications

- E.J. Chory, J.G. Kirkland, C-Y Chang, V.D. D'Andrea, S. Gourinsankar, E.C. Dykhuizen, G.R. Crabtree Inhibition of a Selective SWI/SNF Function Synergizes with ATR Inhibitors in Cancer Cell Killing *bioRxiv* posted June 4, 2019.

Patents

- Published Application: WO2019055657
- Published Application: 20200255416
- Issued: 11,267,809 (USA)

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