Bantam Pharmaceutical
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The good kind of stress

Bantam Pharmaceutical is targeting untapped mitochondrial stress pathways in aggressive tumors, offering hope to patients facing daunting odds.

Relapse and resistance are common with most cancers and can reflect the presence of aggressive cancers on which standard-of-care therapies have little impact. Patients facing an uphill climb following a cancer diagnosis could benefit from novel treatment approaches, but much of biopharma development is focused on modest improvements for established pathways.

Bantam Pharmaceutical, based in Research Triangle Park, North Carolina, United States, has picked up the challenge to develop therapies for hematological and solid tumors, developing a pipeline of small molecules targeting a novel mechanism: mitochondrial homeostasis. "Our therapeutic pathway is unique and orthogonal to other approaches, meaning we expect to see remarkable efficacy as monotherapy and synergistic effects in combination," said Todd Hembrough, a former AstraZeneca executive who now serves as Bantam's translational medicine advisor. "It also means if other therapies fail, we don't expect that to have any impact on this pathway."

"So much of drug development is 'me-too', with multiple companies targeting the latest activating mutation in a particular RTK [receptor tyrosine kinase] target," Hembrough added. "But by focusing resources on stepwise improvements, the whole field winds up trading risk for potential impact."

By contrast, Bantam is developing a new class known as selective modulators of mitochondrial dynamics (SeMMiDs). These target OMA-1, a mitochondrial protein that is part of the integrated stress response pathway. In healthy cells, OMA-1 is an important mediator of cell health from within the mitochondria. But in many cancers, mitochondria are hijacked to meet increased energy needs, becoming a key driver of rapid proliferation. However, OMA-1 protease activation can induce apoptosis under certain conditions via mitochondrial stress signaling through a highly evolutionary conserved process.

Developing an innovative pipeline

The company was founded to develop drugs based on a series of small molecules that showed tremendous preclinical efficacy, but were not suitably drug-like. Bantam has since developed a pipeline of novel molecules with improved pharmacokinetics and pharmacodynamics, including the lead candidate, BTM-3566 (Fig. 1). "We've successfully tested it in multiple cancers, including some aggressive lymphomas. I've never before seen a single-agent drug that can induce complete remission in these," said Adrian Schwarzer, a clinician-scientist at Hannover Medical School in Germany and scientific advisor to Bantam.

Recent discoveries have clarified what makes SeMMiDs so efficacious and, potentially, so safe. Certain cancers appear to be sensitized to the compounds in the absence of another mitochondrial protein, FAM210B, which is abundant in healthy cells but expressed at low levels in numerous cancers and is absent in most lymphomas.

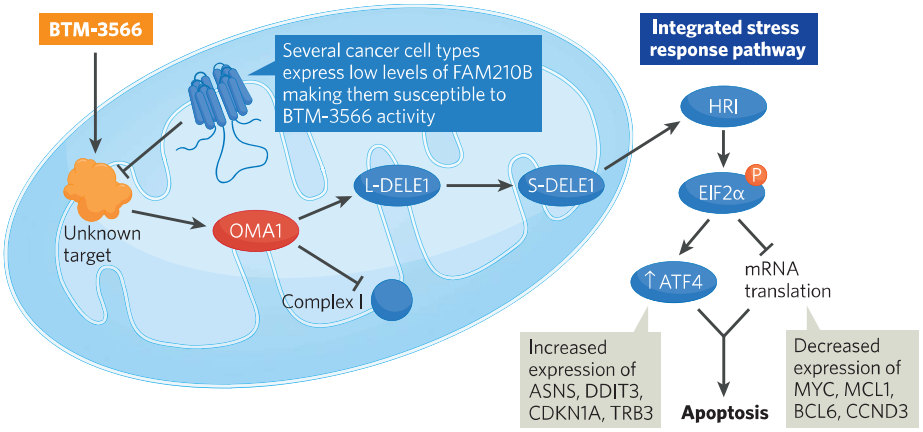

Fig. 1 | Lead candidate BTM-3566 induces apoptosis in B cell malignancies. Modulation of mitochondrial dynamics triggers selective cancer cell death through well-characterized pathway.

"This finding helped us to better understand how the compounds activate a specific mitochondrial stress pathway. It also means we have a biomarker to guide development of therapies targeted to cancers with low FAM210B expression," said Schwarzer.

> **Bantam Pharmaceutical has an open investigational new drug application for BTM-3566, approved by the US Food & Drug Administration, and is now ready to enroll patients**

In humans, mantle cell lymphoma and diffuse large B cell lymphoma (DLBCL) are very likely to respond to BTM-3566, especially double- and triple-hit DLBCL. These have amplifications or translocations of several genes linked to cell growth or anti-apoptotic states, including genes such as MYC, BCL-2 and BCL-6. "These are some of the most difficult-to-treat DLBCL patients," Schwarzer said. "Historically, 90% of patients who progress after first-line therapy die within a year. It's exciting to see that BTM-3566 has exceptional preclinical in vivo activity in these subtypes, leveraging mitochondrial stress to drive apoptosis."

Bantam's targeted approach for selective OMA-1 activation represents unique IP and may be just the tip of the iceberg because disrupting mitochondrial homeostasis is still largely an unexplored therapeutic area. There are four known mitochondrial stress pathways, but as yet there are no approved drugs.

What's next for Bantam?

The company has an open investigational new drug (IND) application for BTM-3566, approved by the US Food & Drug Administration, and is now ready to enroll patients in clinical sites for its phase 1 study. The company is currently raising a series A round to initiate the study designed to establish the optimal dose and clinical proof of concept for the novel mechanism and drug. In subsequent trials, Bantam plans to test the compound in combination with standard-of-care rituximab in lymphoma, and is also exploring combinations with other synergistic molecules in solid tumors and other hematological malignancies.

Bantam expects to have data within 12–18 months of launching its trial, though given the impressive results in multiple patient-derived xenograft models, it hopes to see early evidence of efficacy even sooner. "As someone who has spent a career focused on translation, I recognize that all companies are looking for reasons to believe their approach is going to make a difference in the clinic," Hembrough said. "But we're eager to begin testing this in patients, because we see the potential for much more than incremental advances. The team has been drawn to Bantam by the fantastic preclinical data, and the potential for profound effects in DLBCL subpopulations—and beyond. The phase 1 trial of BTM-3566 is just the beginning."

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