

BioTheryX Inc
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BioTheryX

Degrading proteins, creating life-saving medicines

Biotechnology company BioTheryX develops unique therapeutics for both oncology and inflammatory diseases based upon its novel protein degradation technology platform.

BioTheryX is a results-oriented biotechnology company whose mission is to create novel therapeutics by degrading disease-causing proteins. The company's founders are scientific pioneers who wrote the book on targeted protein degradation with the development of IMiDs, one of the most successful anti-cancer franchises in history. The team at BioTheryX has brought this unmatched expertise to bear in the development of novel therapeutics for oncology and inflammatory diseases. In addition, BioTheryX has a world-class scientific advisory board including 2004 Nobel Laureate, Aaron Ciechanover, a globally-recognized leader in protein degradation who serves exclusively on the BioTheryX scientific board in protein degradation.

BioTheryX's technology platform centers on targeted protein degradation, including PHM 'molecular glues', PROteolysis TARgeting Chimeras (PROTACs/PTCs) and monovalent degraders that enable the design of small molecules to regulate protein equilibrium. This technology is designed to utilize the body's own protein disposal system to

selectively degrade and remove disease-causing proteins (Fig. 1). It has potential applicability to a broad range of diseases, including targets that have to date been considered undruggable (Fig. 2). To protect its technology and pipeline, BioTheryX has an impressive patent portfolio with approximately 85% of its 2,500-plus drug-like compound library protected by 50 issued and more than 140 pending patents.

BioTheryX's science in action

BioTheryX is leveraging its knowledge of Targeted Protein Degradation (TPD) and modulation to rapidly advance its clinical and preclinical stage programs. The company's focus is on high-impact targets, identifying clinically validated biological pathways with key proteins that drive the pathogenesis of multiple diseases that have been difficult to drug with conventional methods. The initial programs target CDK7/9, GSPT1, CK1a, IKAROS, PDE4, and KRAS with the potential to address a broad range of therapeutic areas including oncology, inflammation and other diseases.

"The company's deep pipeline of compounds has been built up over the past five years and is based on some 15 years of scientific and commercial experience with IMiDs," said Robert Williamson, President and CEO of BioTheryX.

The company's lead clinical candidate, BTX-A51, is an oral small molecule, multi-kinase inhibitor designed to block a specific leukemic stem cell target (CK1 α) as well as super enhancer targets (CDK7/CDK9) preventing transcription of key oncogenic genes. This therapeutic mechanism entails activation of p53 (an important tumor suppressor) and its sustained stabilization by super-enhancer shutdown of MDM2 (a protein degrader of p53), in combination with transcriptional shutdown of leukemia oncogenes, including Myc and MCL1.

Blocking CK1 α , CDK7, and CDK9 augments and synergistically stabilizes p53 and down regulates Myc and MCL1 promoting the rapid killing of leukemia cells as well as leukemic stem cells. Pre-clinical results have been published in a peer-reviewed *Cell* journal, demonstrating BTX-A51's

We degrade proteins with three molecular tools

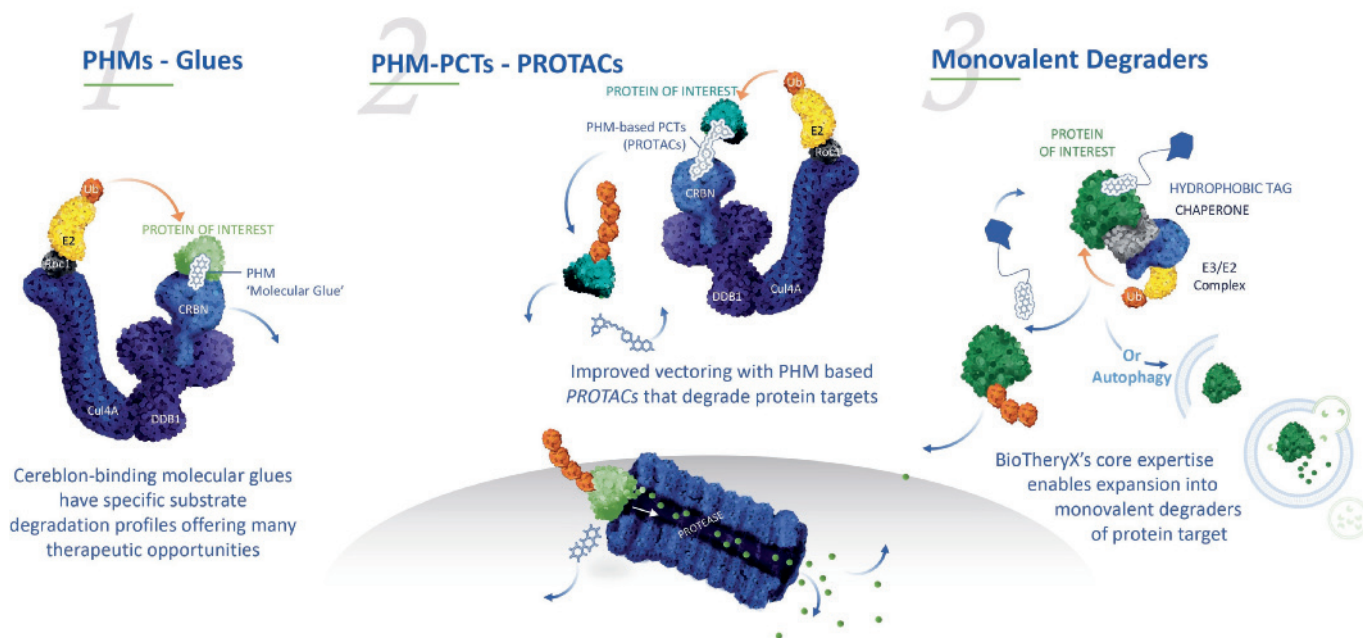


Fig. 1 | Protein degradation tools. BioTheryX can degrade proteins with 3 molecular tools; PHMs (glues), PHM-PCTs (PROTACs) and monovalent degraders. PHM-PCTs, proteolysis-targeting chimeric molecules; PROTACs, PROteolysis TARgeting Chimeras.

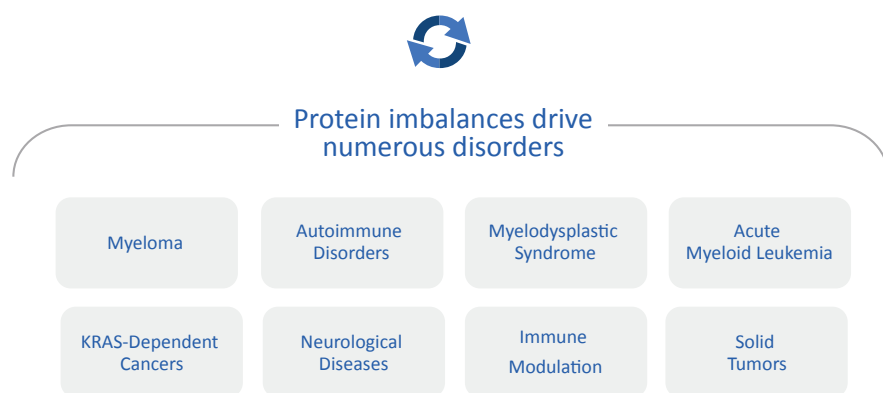


Fig. 2 | Therapeutic potential and opportunity at BioTheryX. With its platform and current portfolio of assets to treat numerous disorders and diseases, such as myeloma and solid tumors, BioTheryX has a broad therapeutic opportunity.

favorable efficacy in animals. The company has commenced phase 1 clinical trials of BTX-A51 for relapsed/refractory acute myeloid leukemia (AML) and high risk MDS in 2020 at the three top oncology sites in the USA, Memorial Sloan Kettering, MD Anderson and City of Hope.

"BTX-A51 appears to block a specific leukemic stem cell target (CK1-alpha) as well as the super-enhancer targets CDK7 and CDK9, preventing transcription of key oncogenic genes," added Williamson. "It may become one of the most important new treatments for AML in the last 40 years. Given the central role of p53, Myc, and MCL1 in cancer progression, the mechanism of action of this molecule may also be applied to solid tumors and other hematologic malignancies."

Beyond the BTX-A51 program, the company's PHM cereblon-modulating molecular glues are designed to reprogram cereblon to degrade specific proteins of interest and have clinically relevant substrate degradation profiles offering broad therapeutic opportunities. In addition, the extensive and unique patented structural classes of PHMs provide a new level of structural control in designing proteolysis-targeting chimeric molecules (PHM-PTCs) that degrade protein targets with a high probability of success.

Kyle Chan, BioTheryX's Chief Technology Officer said, "We believe we know how to manipulate cereblon better than anyone else. We have the ability

to control specific degradation of some important clinically validated substrates. These include targets such as Ikaros, GSPT1 and Aiolos, which are all undruggable targets in a classic sense along with new clinical targets that we have discovered."

BioTheryX's lead program, BTX-A51, in development for AML, MDS and solid and hematologic malignancies

Despite recent advances in AML therapy with agents that target specific genetic mutations, there still remains a significant unmet medical need for therapeutics that can provide deep and durable responses without the early development of resistance. BioTheryX has taken a novel approach to treating these cancers through an innovative mechanism of action with BTX-A51.

BTX-A51 is a multi-kinase inhibitor that targets key pathways of leukemia cell survival, attacking several leukemic proteins simultaneously and making it difficult for leukemic cells to activate other proteins and evade therapy. BTX-A51 inhibits CK1a, CDK7 and CDK9 and turns off the key AML oncoproteins Myc, MDM2 and MCL1, and hyper-stabilizes p53, a gene that is deactivated in many cancers.

If BioTheryX's BTX-A51 is successful in clinical trials, Williamson says the market opportunity for BTX-A51 could be worth more than \$10 billion, with similar market potential to Revlimid, which is effective in myeloma and myelodysplastic syndrome (MDS), but not AML.

BioTheryX's leading molecular glue candidate, BTX-1188

BTX-1188 is a leading PHM molecular glue candidate with strong potential for treating AML and MDS. In vivo efficacy of BTX-1188 was evaluated using the MV-411 human AML xenograft model in athymic nude mice. The study shows a significant reduction in tumor volume with intermittent dosing, further establishing the candidate's potential for AML. Importantly, BTX-1188 completely eliminated the tumors in less than two weeks of dosing and maintained tumor-free animals until the end of the study.

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Robert Williamson,
President and CEO,
BioTheryX

BTX-1188 is expected to be a best-in-class molecule by combining both the potent killing of tumor cells and simultaneous modulation of the immune system, resulting in better efficacy and potentially fewer side effects

Kyle Chan,
Chief Technology Officer,
BioTheryX

Pre-clinical studies also indicated BTX-1188's superior performance over Celgene's CC900009 CELMoD, it showed 100 times greater potency on CC900009 naïve cells, and 2000 times more potency on CC900009 resistant cells and is also a much deeper and durable degrader of GSPT1 than CC90009.

"As opposed to a pure GSPT1 degrader, such as CC90009, BTX-1188 is designed to degrade GSPT1, Ikaros, and CK1a and is expected to be a best-in-class molecule by combining both the potent killing of tumor cells and simultaneous modulation of the immune system, resulting in better efficacy and potentially fewer side effects," Chan said.

Pipeline expansion and future outlook for BioTheryX

Due to its novel approach and robust intellectual property, the company is also open to partnerships around its protein degradation platform to expand upon its deep experience and grow its extensive library of protein degraders, including molecular glues, proteolysis-targeting chimeras and monovalent degraders.

In the near term, the goal is to advance BTX-A51 through phase 1, obtain regulatory approval to initiate clinical studies of BTX-1188, expand the protein degradation platform, and support an IND engine that advances one or two candidates into the clinic annually. In the next several years, BioTheryX plans to increase its platform into other therapeutic areas and E3 ligases beyond cereblon, having multiple shots on goal in oncology and inflammation, and advancing at least three programs toward the market and to address patient needs.

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