
Proceedings Paper:
Bon, RS orcid.org/0000-0003-1733-3680 (2016) Identification of the Molecular Target of an Inducer of Human Glioblastoma Self-Destruction. In: Polson, ES, Kuchler, VB, Beard, HA, Ross, E, Markowetz, F, Zhu, S and Wurdak, H, (eds.) EMBO Chemical Biology symposium proceedings 2016. EMBO Chemical Biology Symposium 2016, 31 Aug - 03 Sep 2016, Heidelberg, Germany. EMBO .

Identification of the Molecular Target of an Inducer of Human Glioblastoma Self-Destruction

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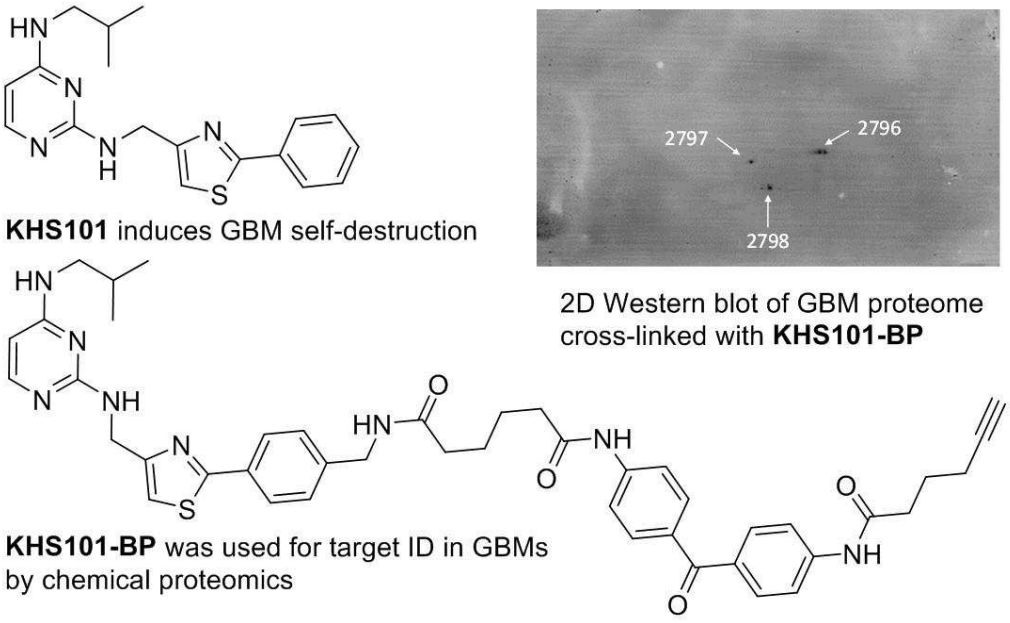
Glioblastoma multiforme (GBM) is the most malignant form of brain cancer in adults with a very poor prognosis despite treatment. [1] The development of novel therapies for GBM is challenging due to its infiltrative nature, the heterogeneous and adaptive/drug-resistant character of GBM cells, and the blood brain barrier. [2] We discovered that the brain-penetrable small molecule KHS101 [3] selectively induces the self-destruction of molecularly-diverse, human patient-derived GBM cells by targeting specific metabolic vulnerabilities. Moreover, KHS101 is effective in orthotopic xenograft models.

We identified the molecular target of KHS101 in GBMs through a combination of gene expression profiling/'connectivity mapping', metabolomics, and chemical proteomics. For the latter, we used a biologically active photo-reactive benzophenone probe (KHS101-BP). Photocrosslinking experiments using KHS101-BP in life cells allowed us to identify a molecular target with direct relevance to KHS101-induced GBM self-destruction. We subsequently developed KHS101 analogues and derivatives incorporating biotin or a fluorophore to enable biophysical characterisation of the interaction between KHS101 and its protein target. These tools may allow the development of assays for rapid screening/optimisation of new compounds for the treatment of GBM.



KHS101 induces GBM self-destruction

2D Western blot of GBM proteome cross-linked with **KHS101-BP**

KHS101-BP was used for target ID in GBMs by chemical proteomics

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