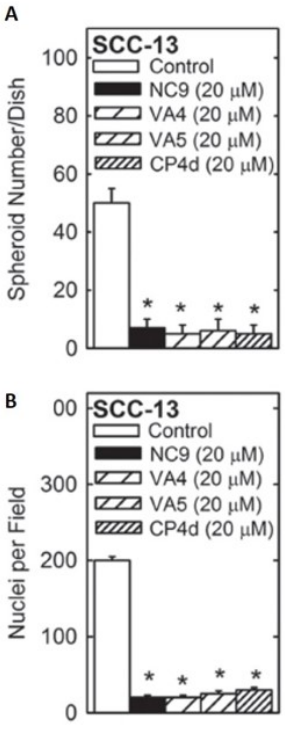
TECHNOLOGY

Irreversible Inhibitors of Type II Transglutaminase

OVERVIEW

Cancer stem cells (CSC) comprise a subpopulation of tumor cells that are slow-cycling, express stem cell markers, display enhanced migratory potential, undergo epithelial-mesenchymal transition (EMT), and form rapidly growing and highly vascularized and aggressive tumors. CSC often survive conventional cancer therapy and proceed to form rapidly growing and highly aggressive and invasive tumors. Studies suggest that type II transglutaminase (TG2) is overexpressed in cancer and associated with aggressive cancer phenotypes, drug resistance, and survival. TG2 expression has been studied extensively in pancreatic, breast, ovarian, epidermal squamous cell carcinoma, prostate, glioma, melanoma, lung, and colon cancer. In these cancers, TG2 levels are markedly elevated and have been shown to affect CSC survival, migration, and invasion. In collaboration with the University of Ottawa, UMB researchers have developed and validated a range of small molecule inhibitors of TG2 and demonstrated their anti-cancer efficacy in epidermal squamous cell carcinoma cell lines.

NC9 is a TG2-selective targeted, covalent inhibitor. NC9 inhibits TG2 by binding to its transamidase site, locking it in a conformation in which the GTP binding site is disrupted and inactivated, thereby abolishing the activity that is required for the pro-cancer and CSC survival activity of TG2. TG2 is highly elevated in epidermal cancer cells (ECS) and TG2 knockdown, as well as treatment with NC9, have been shown to reduce ECS cell survival, spheroid formation and Matrigel invasion and migration, as well as enhanced apoptosis and impaired EMT.



(A) TG2 inhibitors suppress cancer stem cell survival. SCC-13 cells were permitted to form spheroids for eight days before being treated for 48 h with 0 or 20 µM of the indicated inhibitor, and surviving spheroids were counted.

B) TG2 inhibitors reduce SCC-13 cell matrigel invasion. SCC-13 cells were plated on a Matrigel-coated membrane in the presence of 0 or 20 µM of the indicated inhibitor, and after 24 h the cells migrating to the internal side of the membrane were counted.

*The values are mean ± SEM, n=6 (P<0.001)

APPLICATIONS

Commercially-available TG2 inhibitors are not as well-characterized or clinically-relevant as NC9, the lead research compound identified at UMB. Naturally occurring inhibitors do not inhibit human TG2, and most synthetic inhibitors are also potent Factor XIII inhibitors, affecting coagulation. The novel TG2 inhibitors described here show superior *in vitro* selectivity toward human TG2. There is currently one TG2 inhibitor undergoing clinical development, being evaluated for the treatment of Celiac disease. Targeting TG in cancer represents a novel treatment strategy. In addition to their application in cancer, these TG2 inhibitors may be used to study other biological functions and pathology where TG2 is involved, such as autoimmune, inflammatory, and neurological diseases.

ADVANTAGES

Lead TG2 inhibitors provide a potential therapeutic for aggressive cancer phenotypes; utility extends to other conditions with altered TG2 function

STAGE OF DEVELOPMENT

This technology has been tested *in vitro* in squamous cell carcinoma cell lines.

LICENSING POTENTIAL

Available for licensing

Available for sponsored research

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Additional Information

INSTITUTION

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PATENT STATUS

Pending

LICENSE STATUS

Available for licensing; Available for sponsored research

CATEGORIES

- Small molecules

INVESTIGATOR(S)

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ATTACHMENTS

- Download RE-2016-066 Marketing Sheet 5-25-17 FINAL.pdf

EXTERNAL RESOURCES

- Transamidase site-targeted agents alter the conformation of the TG CSC survival protein to reduce GTP activity and CSC survival
- Transglutaminase is a tumor cell and cancer stem cell survival factor

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